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A comparisaon of the incidence and characteristics of psychosis in Palermo and South London

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**A comparison of the incidence and
characteristics of psychosis in Palermo and
South London**

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Thesis submitted for the degree of Doctor of
Philosophy

Institute of Psychiatry
King's College of London
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Abstract

There is consistent evidence that incidence rates of psychotic disorders vary in different geographical areas. The variation of the distribution of a disease can give clues to the role played by different risk factors.

In Italy there are only a few epidemiological studies on psychosis. In this thesis I aimed to contribute by a) widening Italian epidemiological research on the incidence of psychoses and b) investigating the role of some of the putative risk factors associated with this group of disorders.

Results in this thesis are presented in two parts. The first part reports incidence rates of psychoses in Palermo. I collected data on 204 first episode psychosis patients, presenting to the mental health services, over a period of 3 years in a well-defined catchment area of Palermo, Italy. I carried out an incidence study and I calculated crude and adjusted incidence rates of affective and non-affective psychoses. I compared the Palermo incidence data I acquired with the existing UK data from the AESOP study.

My findings were consistent with the literature indicating that there is an increased risk for all psychotic disorders in males and in migrants. Incidence rates of all psychoses in Palermo were lower than in UK except for schizophrenia and the most striking difference was in the likelihood to develop affective psychoses which was significantly greater in UK.

The second chapter of results describes the prevalence of some putative risk factors associated with the development of psychotic disorders, such as cannabis and other illicit drug consumption, family history of psychiatric disorders and psychosis, childhood traumatic experiences, adult adverse life events. I carried out a case control study on a subsample of 68 first episode psychotic patients and a sample of 74 healthy controls representative of the local population.

Family history for psychiatric disorders was more common among patients than controls; cannabis consumption was higher among cases at the time of assessment. Patients were more likely than healthy controls to have

started to smoke cannabis before 15 years of age, and to report a higher frequency of use.

Some experiences (having been injured or assaulted, having experienced having been expelled from school, running away from home, having been forced into authority care) and physical and sexual abuse in childhood were more common among cases than in controls.

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Organization of the thesis

This Thesis comprises a total of 6 chapters.

Chapter 1 is the Introduction that covers, through an examination of the literature, two main topics: the epidemiology of psychotic disorders and the risk factors associated with the development of psychoses.

Chapter 2 describes the aims and the hypotheses.

In Chapter 3 methods and statistical analyses are presented both for the incidence and for the case control parts of the study.

Chapter 4 describes the results about incidence and chapter 5 the results about the case control analyses on the prevalence of risk factors for psychosis.

Chapter 6 summarizes the findings of the research project discussing the results on the basis of the existing scientific data on the topic.

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Chapter 1

Definition, epidemiology and risk factors of psychotic disorders

In this chapter I will describe the concepts of schizophrenia and psychosis and their current classification (paragraph 1.1), the epidemiology of psychotic disorders (paragraph 1.2) and the risk factors (paragraph 1.3). I then focus on the literature about risk factors associated with psychosis that will be explored in this work (paragraph 1.4) and the literature about epidemiology and risk factors in Italy (paragraph 1.5).

To identify relevant papers on epidemiology of psychosis I searched PubMed and PsychINFO from 1980 to January 2015 using the combination of the following search terms: psychosis, incidence, schizophrenia, epidemiology, Italy. The same databases were used to search for papers on the risk factors associated with psychosis combining schizophrenia, psychosis, risk factors, aetiology, and then separately for each risk factor combining the specific key word (e.g. cannabis) and psychosis or schizophrenia. The literature search was then repeated introducing the term Italy or Italian for each risk factor under investigation.

1.1 Introduction

The term psychosis was introduced in the nineteenth century meaning “mental illness”, and indicated a heterogeneous group of diseases characterized by a loss of contact with reality, thought disorders, perceptual abnormalities such as hallucinations, emotional disorders, cognitive deterioration, lack of insight, motor and behavioural abnormalities.

Kraepelin (1896) grouped under the term *dementia praecox* some conditions previously observed by other authors: hebephrenia, catatonia and paranoia. He described *dementia praecox* as a disorder characterized by an early onset, a deteriorating course with cognitive

impairment, delusions, hallucinations, emotional flattening. He distinguished this condition from manic-depressive psychosis.

Subsequently Bleuler (1911) coined the term schizophrenia coming from the Greek word “schizein” “separating” and “frenos” “mind, to indicate a group of disorders not invariably characterized by a cognitive deterioration, but with a common central feature which was the “splitting of psychic functions”. He distinguished primary symptoms (indicated by the “4 As”: autism, associative disturbance, affective blunting, ambivalence) and secondary symptoms (delusions and hallucinations). Schneider (1950) described first rank symptoms in order to better characterize the diagnosis of schizophrenia from other psychotic disorders. The first rank symptoms were auditory hallucinations (commenting voices or arguing voices), thought interference (thought withdrawal, insertion, broadcasting), feelings impulses or acts experienced as being under external control, delusional perception.

People with schizophrenia typically hear voices, often criticising or abusing them. The voices may speak directly to the patient, comment on the patient’s actions, or comment about the patient among themselves; people who hear voices often try to make some sense of these hallucinations, and this can lead to the development of strange beliefs or delusions. Many patients also have thought disorder and negative symptoms (affective flattening, alogia, avolition, anhedonia, attentional impairment) (Picchioni and Murray, 2007).

During the last century operational criteria to define schizophrenia were developed. The first was the Present State Examination (PSE/CATEGO) (Wing, Cooper et al. 1974) based on Schneider’s first rank symptoms; then the Research Diagnostic Criteria (RDC, Spitzer, Endicott et al., 1978), the International Classification of Diseases (ICD-10; WHO, 1992), and the Diagnostic and Statistical Manual of Mental Disorders DSM III, IV and 5 (American Psychiatric Association, 1980, 1994, 2013).

Although many definitions of psychosis have been proposed, the diagnostic boundaries of schizophrenia and other psychosis remain still

uncertain and the categorical distinction between schizophrenia and bipolar disorder is unsatisfactory because of the incomplete knowledge about the aetiology and the pathogenesis of these disorders. Schizophrenia merges on one side with bipolar disorder and on the other with schizotypal and paranoid personality disorder (Murray and Dean, 2008). Sometimes people affected by psychosis show a marked affective component and such conditions are often defined as schizoaffective disorders, but it is not infrequent that people firstly diagnosed as affective psychosis are then re-categorised as affected by schizophrenia.

A new conceptualization of psychosis is based on a “continuum model” according to which psychotic symptoms are on a continuum with normal mental states; recent research has pointed out that psychotic-like symptoms can be experienced by the general health population (van Os, Linscott et al., 2009). It has been observed that first degree relatives of patients affected by a psychotic disorders have a higher probability to show paranoid, schizoid or schizotypal characteristics together with some impairments in cognitive performances at an intermediate level between patients and normal controls (Murray and Dean, 2008).

Schizophrenia onset is frequently placed in late adolescence or early adult life. Males have an earlier onset of schizophrenia than women and show a peak of incidence between 20 and 24 years while females show a peak between 29 to 32 years with a larger number of cases presenting later in life (Lewine 1981; Castle, Sham et al. 1998; Hafner 2003). The AESOP study confirmed an earlier age at first presentation for all psychotic disorders in men (29.6 years) than women (32.6 years) (Kirkbride, Fearon et al. 2006). Females tend to have fewer negative symptoms and a better outcome than males.

Some studies report an earlier age of onset of schizophrenia in those with a family history of psychosis (Albus, Schere et al., 1994; Byrne, Agerbo et al., 2002).

The classification of psychotic disorders depends upon duration, type of symptoms and presence or absence of affective symptoms.

There are two main systems to classify psychotic disorders; the ICD-10 (World Health Organization, 1992) and the DSM 5 (APA, 2013).

These two systems differentiate psychotic disorders according to type and duration of symptoms and to the presence of affective symptoms.

For example in the ICD-10 classification system (World Health Organization, 1992), one month of psychotic symptoms is sufficient to make a diagnosis of schizophrenia while in the DSM 5 symptoms have to last at least six months.

Appendix I shows the current classification of psychotic disorders in ICD-10 which will be used in this thesis as a classification system.

Acute and transient Psychosis (ICD 10) or Brief Psychotic Disorder in DSM 5 lasts no longer than one month.

Schizophreniform disorder in DSM 5 is diagnosed when psychotic symptoms persist between one and six months.

Delusional disorder is characterized by a single delusion or of a set of related delusions which should persist for at least three months (ICD 10) or one month (DSM 5). The delusions may persist and vary in their content (paranoid, hypochondriacal, megalomaniac). Other psychopathology is typically absent except for transient and occasional auditory hallucinations and the subject usually performs well in all the areas not related to the delusion.

Schizoaffective disorders are episodic disorders in which both affective and schizophrenic symptoms are prominent within the same episode of illness, simultaneously, or at least within a few days of each other. Schizoaffective disorder may be of depressive or manic type.

When psychotic symptoms occur only in the context of a mood disorder which does not meet criteria for Schizoaffective Disorder, they are classified as Affective Psychosis.

In the ICD 10, Affective Psychoses include: Bipolar disorder with psychotic features, Major Depressive Disorder with psychotic features, Mania with psychotic symptoms. The presence of psychotic symptoms which do not fit to any of the above categories will be diagnosed as Other

non Organic Psychotic Disorders or Unspecified Non Organic Psychosis in ICD 10.

Table 1 shows the main diagnostic categories of psychotic disorders.

Table 1: ICD-10 diagnostic category of psychotic disorders

ICD-10 diagnostic category of psychotic disorders
Non affective psychotic disorders:
Schizophrenia (F20)
Schizotypal disorder (F21)
Delusional disorder (F22)
Brief psychotic disorder (F23)
Schizoaffective disorder (F25)
Psychotic disorder not otherwise specified (F28–F29)
Affective psychotic disorders:
Bipolar disorder with psychotic features (F31.2, F31.5)
Major depressive disorder with psychotic features (F32.3, F33.3)
Mania with psychotic symptoms (F30.2)

The definition of schizophrenia has changed through the six editions of the Diagnostic and Statistical Manual of Mental Disorders. The DSM IV construct of schizophrenia has a fair reliability and a high diagnostic stability; 80-90% of diagnosis of schizophrenia is confirmed after 1-10 years (Tandon, Gaebel et al 2013).

In the newest version of DSM 5 criteria for the diagnosis of schizophrenia have slightly changed.

The note to criterion A considering bizarre delusions and Schneiderian “first rank” symptoms (conversing and commenting voices) as pathognomonic signs of schizophrenia has been deleted because they are not specific and they do not require special treatments. To confirm the diagnosis of schizophrenia, two of the five symptoms of the criterion A (delusions, hallucinations, disorganized speech, disorganized or catatonic

behaviour, and 5) negative symptoms) must be present, and at least one should be delusions, hallucinations or disorganized speech.

The distinction in subtypes for schizophrenia (paranoid, disorganized, catatonic, undifferentiated, and residual) disappeared because it has been found unhelpful in establishing prognosis and treatment strategies

Catatonia has been conceptualized as a separate diagnosis; it may occur in several conditions so it can be described as a specifier of other disorders “Catatonia associated to another mental disorder” (depression, bipolar disorder or psychotic disorders) or as a symptom in the context of another medical condition: “Catatonic disorder due to another medical condition”. The category “other specified Catatonic Disorder may be used when the underlying condition associated with catatonia is unknown (DSM 5, APA, 2013).

The diagnosis of schizoaffective disorder requires a major mood episode to be present for a majority of the disorder’s total duration after Criterion A has been met. The diagnosis became longitudinal rather than episodic, taking into account the entire course of the disease (Malaspina, Owen et al. 2013).

Delusional disorder has been distinguished from the psychotic variants of obsessive-compulsive disorder and body dysmorphic disorder.

Further, the presence of bizarre delusions no longer represents an exclusion criterion for the diagnosis of delusional disorder; shared delusional disorder is no longer a distinct, separate disorder.

Beside the traditional categorical classification, a dimensional approach has been introduced to help the individual assessment through the course of treatment and to improve the prediction of course and outcome. Section III of DSM 5 includes a dimensional approach to rate the severity of the core symptoms of schizophrenia to capture the important heterogeneity in symptom type and severity expressed across individuals with psychotic disorders (DSM 5, APA, 2013).

The main changes from DSM IV are showed in **Fig 1**.

Figure 1: comparison between DSM IV and DSM 5 diagnostic criteria for schizophrenia (Tandon, Gaebel et al. 2013).

Table 1 Schizophrenia in DSM-5. Changes in diagnostic criteria from DSM-IV.	
DSM-IV criteria for schizophrenia	Proposed criteria for schizophrenia in DSM-5
<p>Criterion A. Characteristic symptoms</p> <p>Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated)</p> <ol style="list-style-type: none"> (1) Delusions (2) Hallucinations (3) Disorganized speech (4) Grossly disorganized or catatonic behavior (5) Negative symptoms, i.e., affective flattening, alogia, or avolition <p>Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other</p> <p>Criterion B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).</p> <p>Criterion C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</p> <p>Criterion D. Schizoaffective and major mood disorder exclusion</p> <p>Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.</p> <p>Criterion E. Substance/general mood condition exclusion</p> <p>Substance/general medical condition exclusion: The disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.</p> <p>Criterion F. Relationship to Global Developmental Delay or Autism Spectrum Disorder:</p> <p>If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).</p>	<p>Criterion A. Characteristic symptoms: (Minor change)</p> <p>Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated).</p> <p>At least one of these should include 1–3</p> <ol style="list-style-type: none"> 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (i.e., diminished emotional expression or avolition) <p>Note: Deleted</p> <p>Criterion B. Social/occupational dysfunction (No change)</p> <p>Criterion C. Duration of 6 months (No change)</p> <p>Criterion D. Schizoaffective and mood disorder exclusion No change</p> <p>Criterion E. Substance/general mood condition exclusion No change</p> <p>Criterion F. Relationship to Global Developmental Delay or Autism Spectrum Disorder – Minor Change</p> <p>If there is a history of autism spectrum disorder or other communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).</p>

1.2 Epidemiology of schizophrenia and other psychoses

Despite its relatively low incidence (e.g. 15.2/100,000), the prevalence of schizophrenia (7.2/1000) (Saha, Chant et al. 2005) is relatively high, because it often starts in early adult life and becomes chronic (Picchioni and Murray, 2007).

For many years it had been thought that the incidence of schizophrenia does not vary much across space and time, but according to more recent data we should replace this dogma with the evidence of a true geographical variation (McGrath, Saha et al. 2004).

The absence of an epidemiological variation would represent an exception rather than a rule for any medical disease; it is well known that different biological and environmental risk factors underlying complex

diseases with a multi factorial aetiology such as schizophrenia play a role in modulating the distribution of the illnesses.

The World Health Organization “Ten country study” (Jablensky, Sartorius et al. 1992) carried out a multicentre study in 8 sites. It found that the incidence of “broad” schizophrenia diagnosed by ICD-9 criteria was significantly different across sites ranging from 16 to 42 per 100,000.

However, when “narrow” criteria were applied, the range decreased from 7 to 14 per 100,000 person/years and, despite the twofold difference, they concluded that there was a uniform incidence of schizophrenia around the world (Sartorius, Jablensky et al., 1986; Jablensky, Sartorius et al., 1987, 1992). This contributed to the spread of a false idea that schizophrenia was considered as an “egalitarian” disorder without differences in terms of sex, time and place.

This myth has been disconfirmed by a systematic review on the incidence of schizophrenia by McGrath and colleagues (2004) examining 158 studies from 32 different countries in the world, showing that schizophrenia is characterized by prominent variation across time and place. Rates of the incidence of schizophrenia fall within a range of 7.7 to 43.0 per 100,000, which is over a fivefold difference. The median value was 15.2 per 100,000 and it is about 40% greater in men than in women, and the rate ratio for males versus females was 1.4 (McGrath, Saha et al 2004). In a review by the same research group, increased incidence rates in migrants compared to native-born population were reported. Higher median estimates were reported for those living in higher latitudes only for males (McGrath, Saha et al. 2008)

Perhaps the most comprehensive epidemiological study so far is the Aetiology and Ethnicity in Schizophrenia and Other Psychosis (AESOP) study (Kirkbride, Fearon et al., 2006); this is a three-centre population-based incidence and case control study of first episode psychosis (FEP), aimed at investigating the variation of the incidence of schizophrenia and other psychotic disorders in terms of place, ethnicity, age and sex. It showed a variation in incidence rates of schizophrenia and other

psychoses in the three study centres in England (London, Nottingham and Bristol); the overall incidence rate for all psychotic disorders was 32.1 per 100,000 persons years across the three centers but it was significantly higher in South London (49.4 per 100,000 persons years) than in Nottingham (23.9 per 100,000 persons years) and Bristol (20.4 per 100,000 persons years), confirming the observation that a higher gradient of urbanicity is associated with an increased risk of developing a psychotic disorder (Kirkbride, Fearon et al 2006).

On the other hand, the Cavan-Monaghan study was carried on in a rural area of Ireland with a homogenous ethnic and socio-economic population characterized by a low social mobility. The incidence of psychotic disorders was 18.7/100,000 persons year (Scully, Quinn et al. 2002).

Further, the incidence of schizophrenia can change over time (Allardyce, Morrison et al. 2000, Al Mousawi, Dunstan et al. 1998, Suvisaari, Haukka et al. 1999, Boydell, van Os et al. 2003). Boydell and colleagues demonstrated that the incidence of schizophrenia in South London doubled between 1965 and 1997. However, Kirkbride and colleagues examined the incidence of psychotic disorder in three different periods of time and they found out a substantial stability in the incidence of affective and non-affective psychoses but an increase of substance induced psychosis (Kirkbride, Croudace et al. 2009).

A recent meta-analyses carried on published data between 1950 and 2009 on the incidence of psychotic disorders in England confirmed the heterogeneity of incidence by sex, age, place and migration status/ethnicity. The authors found that the pooled incidence for all psychotic disorders was 31.7 per 100,000 person years, 23.2 for non-affective psychosis, 15.2 for schizophrenia, and 12.4 for affective psychosis. The authors pointed out that the incidence of psychotic disorders tended to remain stable over the period considered (Kirkbride, Errazuriz et al., 2012).

There are few data on the incidence of Bipolar Disorder. Lloyd and Jones reported a range of 2.6 to 20.0 per 100 000 per year (Lloyd and Jones,

2002). In the AESOP study the overall incidence of Bipolar Disorders across the three centers was 4 per 100,000 per year but in South East London it was more than double than in Nottingham and Bristol and the risk was fivefold higher in African-Caribbean and Black African compared to White people; no differences in incidence rates have been found in men and women (Lloyd, Kennedy et al. 2005).

In San Paulo Brazil, Menezes and colleagues reported an incidence rate of psychoses of 15.8 per 100,000 per year for any psychotic disorder; this was lower than expected for a large metropolis (Menezes, Scazufca et al., 2007).

The geographical incidence variation could be due to the different distribution of environmental and biological risk factors. There is now evidence concerning the role played by social factors such as urbanicity, migration, childhood adversities and social isolation, and by biological factors such as family history of psychosis, obstetric complications, substance abuse, advanced paternal age (Stilo and Murray, 2010). A more detailed description of the risk factors for schizophrenia will follow in this chapter.

1.3 Risk factors for psychotic disorders

Psychotic disorders are currently interpreted as illnesses with a complex aetiology involving both genetic and environmental risk factors.

Risk factors for psychotic disorders can be divided into biological and social (Stilo and Murray 2010).

Among biological factors there are:

- Genetic susceptibility
- Advanced parental age
- Pre and perinatal events often collectively termed obstetric complications
- Viral infections
- Exposure to illicit drugs

Social factors implicated in the development of psychotic disorders are:

- Urbanicity
- Migration
- Childhood adversities
- Adult adversities

Discovering the complex aetiology of schizophrenia is still a challenge.

The two major theories schizophrenia are the neurodevelopmental hypothesis and the dopamine hypothesis. Now the two hypotheses are beginning to integrate: early developmental factors interact with environmental and social pressures during childhood and adolescence and result in dopaminergic dysregulation that ultimately turns normal beliefs into delusions (Murray, Lappin et al. 2008).

The dopamine hypothesis of schizophrenia was proposed over 40 years ago and it states that schizophrenia is associated with an excess of dopaminergic function in the brain. It derives from the evidence that all antipsychotics block dopamine D₂ receptors whereas direct or indirect dopamine agonists elicit positive symptoms of schizophrenia (Murray, McDonald et al 2002).

It has been observed that there is an excess of dopamine release in the striatum of people at ultra high risk of psychosis and in people affected by their first episode of psychosis (Howes, Montgomery et al.2007).

Dopamine dysregulation is now postulated to be one of the final steps in a complex development cascade towards schizophrenia that starts early in life and which may be underlined by different mechanisms such as neurodevelopmental impairment, drug abuse, severe chronic social stress as shown in **Fig 2**.

Different kinds of cerebral damage such as hypoxia, drug exposure, obstetric complications may cause a D2 dopamine receptor high affinity state, determining “dopamine super-sensitivity”. Dopamine super-sensitivity may be responsible for altered responses to environmental stimuli.

Mesolimbic dopamine system mediates the “attribution of salience” of external stimuli, that is the attribution of meaning to ideas and objects (Berridge and Robinson 1998) which will be represented as negative or positive, thus leading goal-oriented behaviour.

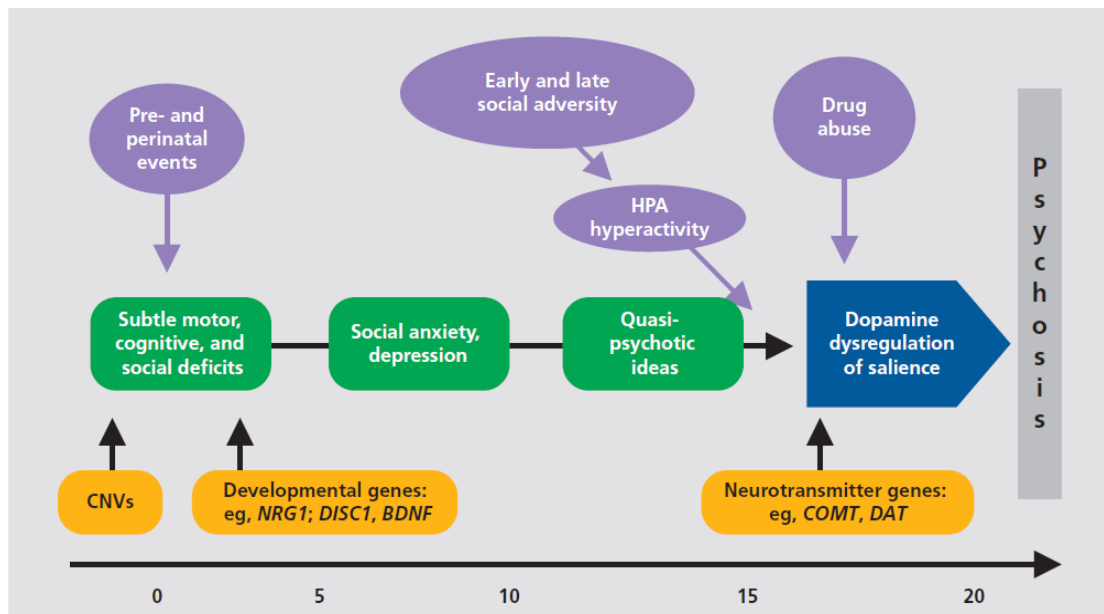
A dysregulated hyperdopaminergic state is suggested to lead to an aberrant assignment of salience to normal stimuli and delusions represent a cognitive effort by the patient to make sense of these aberrantly salient experiences (Kapur 2003).

In animal models, being reared in isolation alters dopamine function in the nucleus accumbens (Hall, Wilkinson 1998). In humans, subjects with a history of low maternal care show a higher release of striatal dopamine when exposed to psychosocial stressors as showed by a PET study by Pruessner and colleagues (Pruessner, Champagne, et al.2004).

Chronic experiences of social adversities may lead to changes in the dopamine system via the hyperactivation of the hypothalamic-pituitary-adrenal axis (HPA) (Lodge and Grace 2011).

Thus, the two major theories of schizophrenia, the neurodevelopmental and the dopamine hypotheses may be integrated conceptualizing a common final mechanism implying a dopamine dysregulation which may be caused by the interplay of different environmental and genetic factors acting indifferent stage of life and finally flowing into a final common pathway (Di Forti, Lappin et al 2007; Howes and Murray 2013) (**Fig. 2**).

Figure 2: the final common pathway towards psychosis (adapted from Stilo and Murray, 2010).



The next two paragraphs present an overview of the biological and the social factors associated to psychosis risk.

1.3.1 Biological factors

Schizophrenia has a **genetic component**. The role of genetic load in the development of psychosis is confirmed by twin studies. Many such studies have been carried out. For example, Cardno and colleagues reported that the concordance rates for schizophrenia in monozygotic twins was 42.6% and that monozygotic co-twins of schizophrenic patients were more likely to develop schizophrenia than the dizygotic co-twins (Cardno, Marshall et al. 1999). Adoption studies showed higher rates of schizophrenia among the adopted offspring of parents affected by schizophrenia than adopted offspring of healthy people (Tienari, 2004).

However it is unlikely that genes directly determine the disease; they are more likely to play a role in creating a susceptibility possibly based on biological deficits; for example the first degree relatives of patients affected by schizophrenia may show subtle biological abnormalities such as delayed P300 potentials, abnormal eye movements, MRI abnormalities and poorer cognitive performances than healthy controls.

Since 2002 a number of susceptibility genes for schizophrenia have been reported. Recent research indicates genetic overlap between schizophrenia and neurodevelopmental disorders. Psychoses may be part of a continuum of a group of neurodevelopmental syndromes such as autism and learning disabilities that result in part from a combination of genetic and environmental effects on brain development and are associated with impairment of cognitive function (Owen, O'Donovan et al., 2011).

Recently a systematic analysis of genome-wide association data by the Schizophrenia Working group of the Psychiatric Genomics consortium found out that genetic risk is conferred by a large number of alleles of small effect. They identified 108 independent genomic loci significantly associated to schizophrenia; genes identified are related to dopamine receptor DRD2 and glutamatergic neurotransmission providing initial clues on the pathophysiology of schizophrenia (Ripke, Neale et al. 2014). Other studies have shown that a small proportion of schizophrenia (possibly about 3%) is due to copy number variants (Kirov, Holmans et al., 2011).

Advanced paternal age is a risk factor for schizophrenia in the offspring (Malaspina, Harlap et al. 2001; Torrey, Miller et al. 1997). Some studies suggest that increased mutations in older paternal germ cells may increase the risk of schizophrenia (Malaspina, Harlap et al. 2001).

Zammit and colleagues (Zammit, Allebeck et al. 2013) tested the hypothesis that premorbid schizoid or schizotypal personality traits of older fathers could represent a confounder of the association of advanced paternal age and schizophrenia but they concluded that older aged fathers did not show more schizophrenic traits than controls, so that the association is more likely explained by a mechanism of DNA aging. On the other hand, there are several recent studies saying that de novo mutations of DNA can't explain the relationship between paternal age and the risk of schizophrenia; some authors concluded that the association between increased paternal age and the risk of schizophrenia depends on the father's age at the time of his first child rather than the age at child

birth disconfirming the putative role of DNA aging (Pedersen, Mortensen et al. 2013).

Population based studies meta-analysis has shown an association between **obstetric complications** and schizophrenia (Cannon, Jones et al. 2002). The obstetric complications can be divided into three categories: complications of pregnancy, abnormal foetal growth and development and complication of delivery.

Exposure to obstetric events especially hypoxia increases the risk of schizophrenia. Such events may impact on the brain structure (Stefanis, Frangou et al. 1999; Cannon, van Erp et al. 2002) and on the dopamine system (El-Khodori and Boksa 2001). Two meta-analyses confirmed the association between obstetric complications and schizophrenia with an OR of approximately 2 (Geddes, Lawrie et al 1995; Verdoux, Geddes et al. 1997).

It has been reported that there is an excess (7-10%) of winter-spring births among schizophrenic patients in the Northern hemisphere (Torrey, Miller et al., 1997). This could be due to prenatal exposure of mothers to **pre and postnatal viral infections** that may impact on foetus development. Prenatal exposure to influenza in the second trimester has been reported to be associated with an increased risk of schizophrenia in the offspring (Mednick, Machon et al., 1988; Byrne, Agerbo et al., 2007) but the results remain inconsistent because they have not been fully replicated in all the research studies.

Other infectious agents may be implied in increasing the risk of developing a psychotic disorder such as rubella, herpes simplex and toxoplasma (Murray and Dean 2008) but these data are controversial; according to Khandaker and colleagues prenatal exposure to herpes simplex or cytomegalovirus is not associated to an increased risk of psychosis (Khandaker, Zimbron, et al. 2013).

Also non infectious environmental conditions as poor maternal malnutrition (Susser, Hoek et al., 1998), diabetes (Cannon, Jones et al., 2002), smoking (Sacker, Done et al., 1995) and rhesus incompatibility

(Hollister, Laing et al., 1996) may increase the risk of developing a psychotic disorder but none of them can be considered as a proven risk factor. A later exposure to infection has been associated to a higher risk of schizophrenia. A recent meta-analysis reported an increased risk of schizophrenia in people exposed to viral infection of the central nervous system (CNS) during childhood; it could be a direct effect of the virus on the CNS or the inflammatory response in the brain (Khandaker, Zimbron, et al. 2012). For example early exposure to Epstein Barr virus (EBV) is associated to psychotic experiences in adolescence (Khandaker, Stochl, et al. 2014).

Imaging studies show structural **brain changes** such as increased ventricular size and decreased cortical grey matter volume especially in the hippocampus, amygdala and thalamus in subjects with schizophrenia in some schizophrenic patients (Wright, Rabe-Hesketh et al., 2000).

These are often present since the time of onset suggesting that they can be the result of abnormal neurodevelopment (Gilmore, 2006; Nosarti, Al-Asady et al., 2002) but some structural changes in the amygdale–hippocampal complex may appear after the onset of psychosis (Velakoulis, Wood et al. 2006) and some structural abnormalities may worsen during the course of the illness.

Pantelis and colleagues demonstrated that subjects at risk for development of psychosis had grey matter abnormalities prior to development of psychosis, but they found additional reductions in grey matter when some of the subjects were rescanned following development of a psychotic illness (Pantelis, Velakoulis et al., 2003).

Job and colleagues found that high risk individuals who later developed schizophrenia showed particular reductions in grey matter in the period immediately prior to development of psychosis (Job, Whalley et al., 2005).

It is still unclear whether structural abnormalities represent ongoing neurodevelopmental and degenerative changes or they are influenced by the antipsychotic treatment (Zipursky, Reilly and Murray 2012). Typical

antipsychotics seem to affect brain morphology to a larger extent compared to the atypicals (Lieberman, Tollefson et al 2005, Dazzan, Morgan et al. 2005). Brain abnormalities may be determined by genetic factors which might impact on the neurodevelopment with a further effect played by environmental factors damaging the brain (Murray and Dean 2008).

Substance abuse (especially stimulants and cannabis consumption) has been associated to an increased risk of developing psychosis.

Drug induced psychosis has deepened the understanding of the complex aetiology of schizophrenia. Research into the effects of LSD provided the basis for the serotonergic model, amphetamines for the dopamine hypothesis, PCP and ketamine for the glutamatergic hypothesis (Paparelli, Di Forti, et al., 2011).

In animal models, repeated exposure to drugs such as amphetamines and cocaine induces dopamine sensitization. Repeated exposure to cannabis induces sensitization to amphetamine in rats (Gorriti, Rodriguez de Fonseca 1999) and some studies suggest dopamine release in humans (Voruganti, Slomka et al 2001).

The availability, type and patterns of illicit drugs abuse vary across different geographical areas; so there might be a difference in the impact of substance of abuse in the development of a psychotic disorder.

Amphetamine-induced psychosis was described in the 1950s (Tatetsu, Goto et al., 1956). It was reported that amphetamine administration produced paranoid states in healthy subjects (Angrist, Sathananthan et al 1974) and could exacerbate psychotic symptoms in schizophrenics (Lieberman, Kane et al., 1987).

The observation that experimental amphetamine administration stimulates the release of dopamine in the striatum and that antipsychotics block psychotic symptoms induced by amphetamines provided the basis for the dopamine hypothesis of schizophrenia (Snyder, 1972).

Also metamphetamine users developed positive symptoms resembling those found in schizophrenia (paranoia, suspiciousness, disorganization

of thoughts, auditory hallucinations, lack of insight, anxiety increased motor activity) (Chen, Lin et al. 2003). Schizophrenia spectrum disorder and amphetamine-induced psychosis seem to share a degree of common vulnerability that may be determined by genetic factors. Chen and colleagues found that the probability to develop a methamphetamine induced psychosis, its duration and severity, were influenced by individual psychosis proneness and family history for psychotic disorders; earlier and greater use was associated to an increased risk (Chen, Lin et al. 2003).

Most cases of metamphetamine psychosis recover after ceasing drug consumption; however in a proportion they do not remit so readily if ever; relapses may occur after a further abuse or even triggered by social stress (Murray, Paparelli et al. 2013). Although amphetamine psychosis has been considered as a distinct entity from schizophrenia, a recent large cohort study found a nine-fold increased risk of developing schizophrenia in metamphetamine users (Callaghan, Cunningham et al 2012).

Amphetamines and metamphetamines probably act via dopamine sensitization; repeated amphetamine administration in healthy humans produces greater dopamine release in the striatum and behavioural response even one year after the first experimental administration (Boileau, Dagher et al. 2006).

According to a recent meta-analysis patients with a first episode of psychosis have a higher prevalence of tobacco use, they start to smoke before the onset and are more likely to smoke than controls (Gurillo, Jauhar et al. 2015).

The association of cannabis exposure and psychosis will be described in details in paragraph 1.4.

1.3.2 Social factors

From the mid-1980s schizophrenia was largely conceptualized as a neurodevelopmental disorder, however during the past decades there

has been a renewed interest in the role played by social factors in the aetiology of psychosis. Urbanicity, migration, childhood abuse and adversities and discrimination represent risk factors for the development of psychotic disorders (Sharpley, Hutchinson et al. 2001; Pedersen and Mortensen 2001; Stilo, Di Forti et al. 2013) even though the exact mechanism by which they increase the risk is still unclear. It is possible that psychosocial factors exerting their role in different stage of life may increase the risk of developing psychosis in vulnerable individuals (e.g. with a genetic susceptibility or with early neurodevelopmental abnormalities). Some suggest that social adversities appear to act in cumulative way e.g. being unemployed, single, living alone having poor education and having no close friends are associated with an increased risk of psychosis (Murray, Lappin et al. 2008).

Urbanicity has been associated with the risk of developing schizophrenia.

In 1939 Faris and Dunham reported higher admission rates of schizophrenia in the most urbanized areas of Chicago. Further, they noted that the incidence was higher in more disorganised areas where people were more isolated (Faris and Dunham, 1939).

Incidence rates of schizophrenia vary within the same country between rural and urban population (Fuller Torrey, Bowler et al. 1997; Allardyce, Kelly et al. 2001; McGrath, Saha et al. 2008) and being born or being brought up in a city increases the risk of developing schizophrenia. There is a dose-response relationship because the larger the town and the longer the individual has lived there, the greater the risk (Mortensen, Pedersen et al. 1999; Krabbendam and van Os 2005; Pedersen and Mortensen 2001). Those differences have not been found for manic depression.

Two main hypotheses have been formulated to explain this phenomenon. One is that of the “drift” hypothesis: it might be that people already prone to develop a psychotic disorder could move in more urbanized and anonymous areas; another explanation is that living in more urbanized

cities exposes the individuals to other risk factors for psychosis such as social isolation and lack of social cohesion.

The urbanicity excess has been confirmed by studies carried on in Northern Europe countries such as in Sweden (Lewis, David et al. 1992), Denmark (Mortensen, Pedersen et al. 1999) and in UK. In the AESOP study the incidence of all psychotic disorders in South London was double than in Nottingham and Bristol (Kirkbride, Fearon et al., 2006; Morgan, Dazzan et al. 2006) and within South East London it was higher in areas with lower social cohesion (Kirkbride, Fearon et al. 2007).

However a recent study run in a rural area in UK (SEPEA study), reported a higher psychosis morbidity than expected: 45.1/100 000 person-years (Kirkbride, Stubbins et al. 2012).

The way urbanicity impacts on the risk of schizophrenia is still unclear but it seems that some factors at an individual (social isolation) (Thornicroft, Bisoffi et al. 1993; Boydell, van Os et al 2004, Morgan, Burns et al. 2007) and at the neighbourhood level (Kirkbride, Fearon et al. 2007) may play a role in increasing the risk.

The other social factors thought to be associated to psychosis risk (migration, exposure to childhood and adult adversities) explored in this work will be described in detail in the next paragraph.

1.4 Risk factors for psychoses on which this Thesis will focus

In this paragraph I will describe in details risk factors associated to psychosis risk which will be explored in this work.

Many studies reported **gender differences** in psychotic disorders. The incidence of schizophrenia is higher among males than females and two meta-analyses showed that the male-female risk ratio was around 1.4 (Aleman, Kahn et al. 2003; McGrath, Saha et al. 2004; Ochoa, Usall et al. 2012).

Data from the AESOP study also report a higher incidence of schizophrenia among men with an incident risk ratio of 2.3, while affective psychoses occurred equally in both sexes (Kirkbride, Fearon et al. 2006).

Gender differences in schizophrenia might reflect the differential proneness of men and women to two different subtypes of schizophrenia presenting in different stages of life; men might be more vulnerable towards neurodevelopmental disorders while women are more likely to develop a psychotic disorder with an affective component than males (Castle, Sham et al. 1994).

Another explanation takes into account the role of protective or precipitating factors; women tend to show a later onset of psychotic disorders and this might be due to the declining of the protective effect exerted by oestrogens (Häfner, Riecher-Rössler et al. 1993; Häfner 2015).

Family history of psychosis in a first degree relative is a well-established risk factor for schizophrenia and other psychosis (Helenius, Munk-Jørgensen et al. 2012). It is a proxy of the genetic load of the disease. The lifetime risk of schizophrenia is higher among first-degree relatives of people affected by the disease (Kendler, McGuire et al., 1993). Patients with a higher familial load of psychosis have an earlier age of onset of the disorder compared to those without (Suvisaari, Haukka et al. 1998).

Patients affected by schizophrenia are also more likely to have one or more first-degree relatives affected by any psychiatric disorder than healthy individuals (Byrne, Agerbo et al. 2002).

There is evidence that the incidence of all psychoses is higher in **migrant** and minority ethnic populations in a number of countries (Cantor-Graae and Selten, 2005; Morgan, Charalambides et al. 2010; Veling and Susser, 2011; Veling, 2013).

In 1932, Ødegaard reported high admission rates for schizophrenia among Norwegian migrants in the US (Ødegaard, 1932). A meta-analysis of population-based studies confirmed a higher incidence of schizophrenia among first generation migrants and ethnic minority groups with a mean relative risk of 2.7 (95% CI 2.3-3.2), especially for black migrants moving to European countries. The risk was higher in people

coming from developing countries and for those who were black skinned among a white population. The relative risk was even higher for second-generation migrants, OR 4.5 (Cantor-Graae and Selten, 2005).

African-Caribbean and Black African people resident in UK show a higher incidence of psychosis when compared to the host population (Harrison, Owens et al., 1988; van Os, Castle et al., 1996; Harrison, Glazebrook et al., 1997; Bhugra, Leff et al., 1997; Sharpley, Hutchinson et al., 2001). In the AESOP study the incidence of schizophrenia across the three centres involved was 9 fold higher in African-Caribbeans and 6 fold higher in Black Africans than in the White British population (Fearon and Morgan 2006); they also found a higher incidence rate for mania in both ethnic groups. However, when incidence studies were carried out in the Caribbean countries, the excess of psychosis for this population found in the UK was no longer observed (Bhugra, Hilwig et al., 1996, Mahy, Mallett et al. 1999).

Higher incidence rates of psychosis have been observed among other ethnic minority groups in the Netherlands (Selten, Veen et al., 2001) in Denmark (Cantor-Graae, Pedersen et al., 2003), in Sweden (Zolkowska, Cantor-Graae et al., 2001) and in Italy (Tarricone, Mimmi et al 2012; Lasalvia, Bonetto et al. 2014).

Other studies have also shown a higher incidence of affective psychosis in migrant groups (Bebbington, Hurry et al., 1981; Lloyd, Kennedy et al., 2005).

However, the increase in the incidence rates for migrant groups disappears when studies are carried out in the country of origin (Bhugra, Hilwig et al., 1996; Hickling, Rodgers-Johnson et al. 1995, Mahy, Mallett et al., 1999); all these data show that migration, and not belonging to a certain ethnic group per se, could represent a risk factor associated to psychotic disorders possibly as a consequence of social discrimination. It has been reported that migrants are especially vulnerable if relatively isolated in localities where their own ethnic group represent a small minority (Boydell, van Os et al., 2001) and this might be explained by an

increased exposure to racial discrimination in areas with low density of an ethnic minority group. Social disadvantage has been associated to the risk of psychosis. In the AESOP study some ethnic minorities such as Black Caribbeans in South East London were more exposed to social disadvantage than White British (Morgan, Kirkbride et al., 2008).

Belonging to an ethnic minority group in a foreign country is postulated to increase the risk of developing schizophrenia probably through the effect of social discrimination and social defeat. Some suggest that exposure to social discrimination for any reason e.g. sexual orientation, appearance or handicap is associated with an increase of psychotic symptoms in general population (Janssen, Hanssen et al. 2003).

Experiences of discrimination may contribute to the creation of a paranoid attributional style that facilitates the development of psychotic symptoms (Garety, Kuipers et al. 2001); even in healthy people, perceived discrimination predicts the development of psychotic symptoms (Janssen Hanssen et al. 2003).

Recent studies suggest **childhood adversities** such as physical, sexual, psychological abuse and neglect represent risk factors for the development of psychotic symptoms. Parental loss or permanent separation from parents before age 16 is associated with a more than threefold increase in the risk of developing psychosis in adulthood (Morgan, Kirkbride et al 2006); living in a single-parent household (Wicks, Hjern et al., 2005) or being institutionalised (Bebbington, Bhugra et al., 2004) increase the risk.

According to the World Health Organization (WHO), child maltreatment includes all forms of physical and emotional maltreatment, sexual abuse, neglect, and exploitation that result in actual or potential harm to the child's health, development or dignity. Within this broad definition, five subtypes can be distinguished – physical abuse; sexual abuse; neglect and negligent treatment; emotional abuse; and exploitation (WHO, 1999). Unfortunately these kinds of abuse often coexist.

There is still some controversy about child abuse being a risk factor for psychotic disorders. Several large population-based studies have found associations between various types of early trauma and psychosis-like experiences in adulthood and others have reported a relatively high prevalence of childhood abuse in samples of patients with psychotic symptoms (Fisher, Morgan et al. 2009). Three reviews analysed the association between childhood abuse and psychosis. Read and colleagues found a prevalence of either sexual and physical abuse of 59% in males and 69% in females affected by a psychiatric disorder (Read, van Os et al. 2004), however Morgan and Fisher (2007) recalculated the weighted prevalence focusing only on those studies considering psychotic patients and excluding adolescents. They found a lower prevalence of either one or another type of abuse of 50% in both males and females. Girls were more exposed to sexual abuse, while the prevalence of physical abuse was almost the same in males and females. They concluded that the evidence for a role of childhood trauma on psychosis was controversial also because of methodological limitations of previous studies. The impact of the abuse experience in childhood may be influenced by gender. Fisher and colleagues report an association between severe physical and sexual abuse and the risk of psychosis in women but not in men (Fisher, Morgan et al. 2009). They also indicated a specificity of the type of abuse, finding that patients affected by psychosis were 3 times more likely to report severe physical abuse from their mothers compared to healthy controls (Fisher, Jones et al., 2010).

Two recent meta-analyses support the association between childhood adversities and psychosis (Matheson, Shepherd et al. 2012; Varese, Smeets et al. 2012). Varese and colleagues reported an increased risk of developing psychosis when children were exposed to traumatic experiences (abuse, neglect, parental death, bullying) with an OR of 2.8 excluding parental loss; Matheson and colleagues confirmed this association finding an OR of 3.6. These meta-analyses failed to find specificity for different types of adversities.

Several studies report that when an individual is exposed to an increasing number and frequency of abuse, there is a dose-response mechanism in increasing the risk of developing psychosis (Janssen, Krabbendam et al. 2004; Shevlin, Houston et al., 2008).

Recent research focused on the role of the exposure to bullying during childhood and the risk of psychosis. Bullying is a common form of early victimisation and it is associated with a wide range of mental health problems in adolescence (Arseneault, Bowes et al., 2010) as well as sub-clinical psychotic symptoms (Arseneault, Cannon et al., 2011; Campbell and Morrison, 2007; Fisher, Schreier et al., 2012; Lataster, van Os et al., 2006). However the association of being bullied in childhood and psychosis risk is still controversial. Trotta and colleagues observed that people affected by a first episode of psychosis were more likely to report bullying victimisation when compared to healthy controls (Trotta, Di Forti et al., 2013).

The mechanism by which childhood trauma increases the risk of psychosis is not completely understood yet. One hypothesis is that child abuse produces enduring changes in the Hypothalamus-Pituitary Adrenal (HPA) axis which interacts with the dopamine system.

Research has been complicated by the fact that it is not easy to have a precise estimate of the abuse occurring in the general population because only a small proportion of maltreatment is regularly reported to the authorities (Theodore, Dunyan, 1999). The World Report on Violence and Health (WHO, 2002) state that childhood sexual abuse occurs in 20% of women and in 5-10% of men (Finkelhor, 1994). There are some variations in the diffusion of the phenomenon that are context and culturally based.

According to the vulnerability-stress model (Nuechterlein and Dawson, 1984), stressful events may play a role in the onset of psychiatric symptoms.

Data from the Camberwell Collaborative Psychosis Study confirmed an excess of **life events** preceding the onset of psychoses of all types (Bebbington, Wilkins et al., 1993).

Life events, defined as situations that bring about a positive or negative change in personal circumstances or involve an element of threat, are associated to increased relapse rates and exacerbation of symptoms in psychotic patients (Bebbington, Wilkins et al. 1993; Ventura, Nuechterlein et al., 2000) and may trigger psychotic symptoms in general population (Johns, Cannon et al 2004; Wiles, Zammit et al., 2006). In the second British National Survey of Psychiatric Morbidity, Bebbington and colleagues found a higher prevalence of victimization experiences (sexual abuse, bullying, to be taken into local authority care, violence at home or at work, running away from home, time spent in a children's institution, being expelled from school, being homeless, having experienced serious illness, injury or assault) among people affected by psychotic disorders. They found that some of these experiences were associated to psychotic disorders. The highest risk was reported for sexual abuse (Bebbington, Bhugra et al., 2004).

A recent meta-analysis of 16 studies confirmed a positive association between adverse adult life events and onset of psychotic disorder with an overall weighted OR of 3.19. Further, adverse life events were associated to the occurrence of psychotic symptoms in the general population. In the clinical studies, cases affected by psychosis were 2 to 8 times more likely to report life events in the period preceding the onset, ranging from 3 months to 3 years prior to the onset (Beards, Gayer-Anderson et al., 2013).

The mechanism by which the exposure to life events may increase the risk of psychosis is not fully understood. There can be an influence of stressful events on the hypothalamic-pituitary adrenal axis HPA and subsequently on the dopamine system or there might be a genetic-environmental interaction between stress and genetic susceptibility

(Howes and Murray, Lancet 2014). Further studies are needed in order to clarify the nature of this association.

Cannabis exposure has been associated to an increased risk of developing psychosis. Cannabis is the most popular illicit drug worldwide and it has been considered a “light” drug for many years. Although most people who smoke cannabis do not become psychotic, evidence from the literature supports an association between cannabis use and an increased risk of developing a psychotic disorder (Henquet, Murray et al. 2005; Moore, Zammit et al 2007).

The main psychoactive component of cannabis is delta-9-Tetrahydrocannabinol (THC); it is responsible of the psychotogenic effect of cannabis. The other main constituent of cannabis is cannabidiol (CBD) which has anti anxiety and antipsychotic properties, and seems to “balance” the psychotogenic effect of THC (Di Forti, Morgan et al., 2009; Bhattacharyya, Morrison et al., 2010).

Recently, high potency varieties of cannabis such as “skunk” have become available in the market over much of Europe. Such varieties of cannabis contain a high concentration of THC and a lower proportion of CBD which seems to “balance” the psychotogenic effect of the former (Di Forti, Morgan et al., 2009; Bhattacharyya, Morrison et al. 2010).

Cannabis intoxication can cause brief psychotic episodes or may exacerbate pre-existing psychotic symptoms (Thorncroft 1990; Mathers and Ghodse 1992). It has been shown that healthy people who are administered THC intravenously were more likely to develop transient psychotic like experiences and that THC worsens psychotic symptoms in people suffering from psychosis (D’Souza, Perry et al. 2004). THC exerts its psychotogenic role by modulating the dopamine neurotransmission, involved in development the psychotic symptoms.

The first report suggesting that cannabis might be a risk factor for psychosis was the Swedish Conscript study. This was a 15 year follow up of a cohort of 45.570 conscripts into the armed forces. The risk of schizophrenia was 2.3 fold higher among subjects who had used

cannabis by 18 years and there was a dose response relationship as the risk of developing schizophrenia was even higher in those who had smoked cannabis more than 50 times (Andreasson, Allebeck et al., 1987).

A series of cohort studies have shown that cannabis use generally predates the psychosis (Arseneault, Cannon et al., 2002, 2004; Zammit, Allebeck et al., 2002; van Os, Bak et al., 2002; Fergusson, Horwood et al., 2003). The Dunedin cohort study showed that children and adolescents who had used cannabis by the age of 15 years were 4.5 times more likely to develop schizophreniform psychosis at the age of 26 years (Arseneault, Cannon et al., 2002).

van Os and colleagues reported a three times higher risk of developing psychotic symptoms in the general population associated to cannabis consumption in the NEMESIS study (van Os, Bak et al. 2005)

Two meta-analyses (Henquet, Murray et al. 2005; Moore, Zammit et al. 2007) concluded that cannabis consumption was associated with approximately two-fold increased risk of developing a psychotic disorder. Individuals who had shown any evidence of psychosis proneness appear especially vulnerable, as those who start use of cannabis in early adolescence. A meta-analysis by Large and colleagues supported the association between cannabis consumption and an earlier age at first presentation of psychosis (Large, Sharma et al., 2011). Other studies confirmed that cannabis use is associated to an earlier age at first presentation of schizophrenia and that there is an interaction between cannabis use and gender difference in age at first presentation; the difference by gender in age at first presentation is reduced in cannabis users (Donoghue, Doody et al., 2014).

Recent evidence shows that high potency cannabis and higher frequency of use are associated with a higher risk of developing psychosis (Di Forti, Morgan et al., 2009).

Only a small proportion of cannabis users develop psychotic symptoms or schizophrenia. It is thought that some individuals may have a genetic

susceptibility to develop psychosis if they are cannabis users; for example they might be carrier of particular polymorphism in candidate genes which are implied in the dopamine neurotransmission or catabolism. An initial finding reported an association between exposure to cannabis and a functional polymorphism in the COMT gene, which has a role in the catabolism of dopamine in the prefrontal cortex (Caspi, Moffitt et al., 2005; Henquet, Rosa et al., 2006).

Other studies report the role of a polymorphism of the gene AKT1, involved in the dopamine neurotransmission in influencing the risk of cannabis use in causing psychosis (Thiselton, Vladimirov et al., 2008; Bolog, Kiss et al. 2012; van Winkel, van Beveren 2011; Di Forti, Iyegbe et al 2012). However these results need to be further replicated.

1.5 Incidence and risk factors of psychosis in Italy

In Italy there are few available data on the incidence of psychotic disorders.

A case register study carried out in Verona, Italy, reported an incidence of schizophrenia and related psychoses of 11 per 100,000 person/years.

Data were collected by the South-Verona Psychiatric Case Register (PCR) over a ten-year period (1979-1988). The rate of schizophrenia and other functional psychoses was 9.9 per 100,000 per year. Rate of affective psychoses was 4 per 100,000 per year which was lower than those reported by other case-registers in Europe suggesting that this could possibly be due to a major role in the treatment of affective disorders carried out by Italian general practitioners (Tansella, Balestrieri et al. 1991).

Another case register study conducted over a 8 year period (between 1982 and 1989) in Portogruaro, in north-eastern Italy, collected information on the access to mental health services (inpatient services, community services, private mental hospitals and forensic hospitals) by the residents aged 15-64 years affected by schizophrenia and other non affective psychosis. The authors reported incidence rates for

schizophrenia of 17 per 100,000 per year for both males and females considering first ever contact with psychiatric services. Males had an earlier contact with psychiatric services compared to females but there were no differences in incidence rates by gender (de Salvia, Barbato et al. 1993). This study did not report the incidence for affective psychotic disorders.

Case register studies have been useful tools in psychiatric epidemiology. They are suitable for relatively rare disorders but they have some limitations: information quality may be influenced by the lack of standardized assessment and the diagnosis might be unreliable (Perera, Soremekun et al. 2009).

Preti and Miotto (2000) reported first admission rates to Italian psychiatric wards of patients affected by schizophrenia, affective psychoses and other non-affective psychoses. They used first admission rates as an estimate of incidence rates over a ten-year period (from 1984 to 1994). They reported a rate of schizophrenia ranging from 6 to 8.8 per 100,000 person/year, from 5.7 to 7.8 per 100,000 for other non-affective psychoses, from 3.3 to 8 per 100,000 for affective psychoses. However this study is based on data published on the Italian National Institute for Statistics (ISTAT) in the health-care statistics yearbooks; as the authors outlined, they reported just a crude measure of incidence based on admission to psychiatric services and they were aware about the possible underestimation or overestimation of true rates and about the unavailability of age and gender standardised rates. They also pointed out an excess of admission rates for schizophrenia compared to those of depressive disorders, as an opposite trend respect to other countries admission rates. They hypothesized that patients affected by depression could be more likely admitted to private mental health facilities or to non-psychiatric structures (Preti and Miotto, 2000).

More recently, two studies reporting incidence rates have been published. These studies collected data on patients affected by a first episode of any psychosis disorder presenting to a well-defined catchment area.

The Psychosis Incident Cohort Outcome Study (PICOS) is a multi-site population based first episode psychosis study carried out in Veneto region in northern Italy. The authors found an incidence of psychotic disorders of 18.1 per 100,000 per year. Incidence rates were 5.6 per 100,000 per year for schizophrenia, 3.8 per 100,000 per year for affective psychoses, 14.3 per 100,000 per year for other non affective psychoses. They also found that the incidence rate for all psychoses was higher in young people and migrants; they did not find any gender differences for all psychosis except that schizophrenia was more common in males (Lasalvia, Bonetto et al. 2014).

Another study in Italy is the Bologna FEP study (BoFeP), an 8-year prospective study reporting an incidence of 16.4 per 100,000 for psychotic disorders (Tarricone, Mimmi et al. 2012) and 7.3 per 100,000 for schizophrenia. Like other international first episode psychosis studies the authors found a higher incidence in young people, in migrants and in males.

The BoFeP and the PICOS studies both reported an increased risk of psychosis in migrants. In Bologna migrants had an increased risk of developing a psychotic disorder when compared to local population (IRR: 2.5, 95% CI 2.2-2.9) (Tarricone, Mimmi et al. 2012); in Veneto the risk ratio for migrants was 2.3 (95% CI 1.8-2.7) (Lasalvia, Bonetto et al 2014). The limitation of these studies is that they did not apply a standardization procedure in order to allow a comparison between incidence rates with other Italian or European sites.

In Italy there are only a few studies on risk factors associated with first episode psychotic disorders. Tosato and colleagues (2013) reported an association between cannabis consumption in first episode psychotic patients and an earlier age of onset (Tosato, Lasalvia et al. 2013). Another Italian study, the BoFePs study reported an association between cannabis and an earlier onset of psychosis after controlling for the effect of other drug; they also reported an earlier age of onset of psychosis in

males who used other psychoactive substances (Allegri, Belvederi et al 2013).

However both studies do not report a comparison of patterns of cannabis use between patients and a healthy control sample.

In sample of 285 first episode schizophrenic patients at their first admission to a psychiatric ward in Milan, 34.7% had a lifetime history of substance abuse and most of those who have used illicit drug had a history of cannabis consumption (80%). Substance abusers had an earlier age of onset and a different symptom presentation (higher scores in thought disturbance and hostility) than non-abusers (Mauri, Volonteri et al. 2006).

As far as I know only one study explored the association between exposure to early trauma and psychosis in Italy.

In a case control study, Rubino and colleagues (2009) found that early childhood traumatic experiences (any kind of emotional, psychological, physical, or sexual abuse before the age of 17 years) increased the risk of schizophrenia by six-fold in a sample of 174 patients affected by schizophrenia, with a dose response pattern (considering the frequency of abuse and the sum of different types of abuse). They reported an effect of physical abuse on schizophrenia risk OR: 1.5 (95% CI: 1.17–1.82), while they did not find an increased risk for sexual abuse. They also found a six-fold increase of the risk for schizophrenia in those who had at least one parent affected by any psychiatric disorder. Parental separation before 16 years was not associated to an increased risk of schizophrenia after controlling for parental discord (Rubino, et al. 2009).

It is clear from the above that it would be valuable to widen the knowledge of the epidemiological distribution of psychosis in different Italian sites by including a study from the south of Italy; also it would be useful to replicate previous findings from other European studies on the role and the distribution of several risk factors implicated in psychosis.

Chapter 2

Aims and Hypothesis

2.1 Introduction

I will now clarify the aims of my thesis.

2.2 Aims

The main aims of this project are:

1. To calculate the incidence of new cases of psychosis presenting to the identified Palermo Mental Health Services over a period of three years (2008-2011) using the local population census data as the population at risk.
2. To identify subgroups at higher risk of psychoses (e.g. migrants versus native Italians, males versus females).
3. To compare the newly acquired Palermo incidence data with the existing UK ones from the AESOP study (Kirkbride, Fearon et al. 2006).
4. To identify the impact of genetic (using family history of psychiatric disorders as a proxy) and environmental risk factors such as cannabis consumption, other illicit drug abuse, migration, childhood traumatic experiences, adult stressful life events in the FEP Palermo sample.
5. To compare the prevalence of the environmental risk factors associated with psychosis in Palermo sample to other first episode studies analyzing the same risk factors (Genetic and Psychosis study, GAP; and Aetiology and Ethnicity in Schizophrenia and Other Psychoses AESOP study).

The results of the thesis will be presented into two separate chapters. The fourth will focus on incidence data and it will cover the first three points; the fifth will describe the results of a case control analysis performed in a subgroup of FEP compared to healthy controls to investigate the distribution of risk factor for psychosis (see the next chapter for a detailed methodological description).

2.3 Hypothesis

2.3.1 Hypothesis for the incidence study

I will test the following hypotheses:

1. I expect similar incidence rates of psychoses when compared to those reported in other Italian sites (Lasalvia, Tosato et al. 2012, Tarricone, Mimmi et al., 2012; Lasalvia, Bonetto et al. 2014),.
2. I expect to find an increased risk of psychosis in some subgroups (males and migrants).
3. I expect lower rates than those reported in UK in the AESOP study.

2.3.2 Hypothesis for the case control study

1. Family history of psychiatric disorder: I expect a higher prevalence of psychiatric and psychotic disorders in first-degree relatives of patients when compared to relatives of healthy controls.
2. Cannabis consumption: I expect a different pattern of cannabis consumption between cases and controls. I expect cases to report a higher exposure to cannabis (e.g. frequency of cannabis use, total number of times of cannabis consumption).
3. I expect an excess of childhood traumatic experiences (separation or death of a parent, physical and sexual abuse) in cases compared to controls.
4. I expect at least some of the victimization experiences to be more common in the group of cases than controls.

Chapter 3

Methods

3.1 Introduction

In this chapter I present the design of 1) an incidence and 2) a case control study on patients at their first episode of psychosis, run in Palermo, the capital of Sicily (Italy), between 1 May 2008 and 30 April 2011.

This work was born because of the interest in, and thanks to the collaboration with two research studies run at the Institute of Psychiatry, King's College of London: the Genetic and Psychosis (GAP) study and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study.

AESOP is a multi-centre population based incidence and case control study conducted in South East London, Nottingham and Bristol over a period of 3 years (1997-2000) on patients with their first episode of psychoses (ICD-10 F20-F29, F30-F33; World Health Organization, 1992) (Kirkbride, Fearon et al. 2006).

GAP is a case-control study, conducted over a period of 5 years (2005-2010) on patients affected by a first episode of psychosis who presented to psychiatric services in South East London (Di Forti, Morgan et al., 2009).

GAP and AESOP studies were focused in identifying the role of cannabis, social adversities and ethnicity in the risk for psychotic disorders.

In 2008 the Psychiatric Section of Palermo University Department "Biomedicina Sperimentale e Neuroscienze Cliniche" (Bionec), started the Sicilian Genetic and Psychosis (SGAP) project, an incidence and a case control study aimed at collecting epidemiological data on the incidence of psychotic disorders in Palermo and at identifying the role of putative environmental and genetic risk factors in the risk of developing psychoses.

In 2010 the Palermo research team and I joined one of the large European first episode psychosis study: “the European network of national schizophrenia networks studying gene-environment interaction study (EUGEI)”. This is an ongoing multi-centre European study investigating the interaction between genetic and environmental factors potentially involved in increasing the risk of schizophrenia and other psychotic disorders (www.eu-gei.eu).

In this thesis, I discuss separately the incidence and the case-control parts of the study. I define the catchment area and I outline screening, recruitment and assessment procedures to identify cases, controls and the population at risk.

I describe statistical analysis and power calculations and my personal contribution to the collection and the analysis of the data. Results for incidence and case control analysis are reported into two separate chapters.

While presenting the results in my sample, I discussed the most striking similarities and differences comparing Palermo data to AESOP and GAP studies looking at differences or similarities in the incidence of psychotic disorder and in the distribution of environmental risk factors across the two samples of first-episode psychosis patients.

3.2 Incidence of psychosis in Palermo

3.2.1. The population at risk

Palermo is an urban area and it is the fifth Municipality in terms of number of residents in Italy.

The incidence of psychotic disorders will be calculated using as a denominator the “population at risk” that is all the people resident in Palermo aged 18-65 years over a period of 3 years (between 1 May 2008 to 30 April 2011).

To obtain the most accurate data on the population at risk, I used the last census data run in 2011 in Italy by the National Institute of Statistics (Istat, 2011).

According to ISTAT, there were a total of 427,913 residents aged 18-65 (207,552 males and 220,361 females) in Palermo in 2011.

The population is largely homogenous in terms of ethnicity that is mostly white Caucasian.

During the last decade, the population of migrants resident in Italy had a threefold increase. However, migrants tend to live in the northern regions of Italy (1.356.937 in North-West; 1.066.393 North-East) rather than southern Italy (338.871) or the Islands (Sicily and Sardinia: 140.655) (Istat, 2011). This might be explained by the differences in the chances of getting a job between northern and southern Italy. In 2011 the unemployment rate in the north of Italy was 5.8% while in the south it was 13.6% (Istat, 2011).

The annual report of statistics of Palermo Municipality, at the end of 2011 reported that 4.2% of the total population in Palermo was foreign (SISTAN, 2012). In this thesis I will term "migrants" all the people who originally born outside Italy.

According to the definition of the 15° census, the term migrant refer to people who were born abroad who live in Italy. Migrants can have Italian citizenship but they are still defined as migrant because the term refers to people who were born outside Italy.

Most of the foreigners in Palermo are first generation migrants, and males are more represented than females.

Second generation migrants (people under 18 who were born in Italy from foreign parents) comprised 3684 people.

35.1% of the foreigners in Palermo come from Middle-Southern Asia, 16.8% from other European countries, 12.8% from Northern Africa, 11.1% from Western Africa, 9.9% from Eastern Asia, 6.4% Eastern Africa.

The most represented ethnic groups come from Sri Lanka (16.3% migrants), followed by Bangladesh (15.7%) and Romania (10.2%) (SISTAN, 2012).

In 2011, 80% of migrants in Palermo were 18-64 years old according to the last census (15° general population census statistical information, n°4/2012).

In terms of the at risk population, migrants aged 18-65 years resident in Palermo at 1° January 2011 were 15,142 (7600 males, 7542 females) and they represented the 3.5% of the resident population.

3.2.2.The catchment area

The catchment area was the whole city of Palermo. All the inpatient and outpatient units of the Palermo Mental Health Department and all the private hospitals in Palermo were included in the study.

Palermo is served by a number of mental health services: all inpatient units (five), private psychiatric hospitals (four) and outpatient services (five) were examined in order to evaluate the incidence of psychosis in Palermo. During this period one inpatient unit closed and another one was opened, so that the numbers of beds available in the catchment area did not change significantly; a private hospital initially serving part of the catchment area closed after one year and it was not replaced by any service.

The five inpatients and the five outpatients units are part of the public regional mental health service system (Azienda Sanitaria Provinciale of Palermo (ASP), Azienda Ospedaliera Universitaria Policlinico, Azienda Ospedale Civico ARNAS, Azienda Ospedali Riuniti Villa Sofia and Ospedale Cervello) while 4 private hospitals (Villa Margherita, Villa Serena, Casa di Cura d'Anna, Casa di Cura Stagno) are private psychiatric clinics which are in the network of the regional public mental health system. All people can receive care in both public and private units because they do not have to pay to receive psychiatric care.

The term “private” also refers to those patients who seek help from private psychiatrists in outpatient settings. Individual private psychiatric

care was not included in the study because there is not any official register of private care and it would have been hard to detect patients in these settings. However, patients affected by a first episode of psychosis under antipsychotic treatment usually need a prescription by public mental health services to get medications as otherwise antipsychotics would be too expensive; so most of the patients who are in the care of private psychiatrists have at least one access to mental health services.

3.2.3 Case definition

Cases were defined as all the people resident in the catchment area, aged 18-65 years and affected by a first episode of psychosis who made contact with mental health services within a period of three years (1 May 2008- 30 April 2011).

Age at first onset was defined as the age the subject had at the time of the first access to psychiatric services.

Several definitions of age of onset have been used in epidemiological studies: age at first admission, age at first consultation, or age when first symptoms or first positive symptoms are manifest. This may lead to discrepancies in the reported age of onset across different studies (Eranti, Maccabe et al. 2013).

As in previous first episode studies (Sartorius, Jablensky et al. 1989; Kirkbride, Fearon et al. 2006), in this work age of onset was defined as the age the subject was at the time of the first access to psychiatric services for psychosis symptoms.

The inclusion criteria for cases were very similar to those of the AESOP and EUGEI except for the age. In AESOP the age of patients was 16 to 64, in EUGEI 18 to 64. In Palermo the age of cases was 18 to 65 although no patients aged 65 have been recruited.

Cases were included if they met the following criteria:

1. Presence of symptoms of any psychosis such as delusions, hallucinations, thought disorder, bizarre or disturbed behaviour, negative symptoms, mania.
2. Residence in the catchment area.

3. First ever contact with psychiatric services for psychotic symptoms.
4. Age between 18 and 65 years.
5. Absence of an organic cause of psychosis and severe learning disability.
6. Diagnosis of ICD-10 criteria for schizophrenia (F20), other non-affective psychoses (F21-29) or affective psychoses (F30-33).

Cases were excluded if they met any of the following criteria:

1. Presence of an organic cause underlying psychotic symptoms.
2. Residence outside the catchment area
3. Previous contact with mental health services for an episode of psychosis.
4. Age under 18 or over 65.
5. Presence of psychotic symptoms resulting from acute intoxication as defined by ICD-10 criteria.

3.2.4 Case ascertainment

A screening was run on all the subjects aged 18-65 years with a first episode of psychosis (defined as the first contact with any psychiatrist) presenting from 1 May 2008 to 30 April 2011 at the mental health services of the catchment area. Each mental health service was contacted on a weekly basis.

It is useful to clarify how the mental health care works in Italy as there are some differences from UK. The pathways to care also differ from region to region within the country.

From a recent multi-centric study, in Italy 33.8% of psychiatric patients have a direct access to mental health care, 20.3% are referred by general hospitals, 33% by general practitioners and 9.8% by private psychiatrists (Volpe, Fiorillo et al. 2013).

There are two main pathways to access to mental health service for a first episode psychotic patient in Palermo. If the patient presents an acute psychotic episode, which can be associated to behavioural disorders, he will be more likely to access an emergency room of a

general hospital and then referred to a psychiatrist. If the symptoms are less acute he might be referred to one of the outpatient units of the general mental health care by his GP. The family is almost always involved in the care of the patient since the first stages.

The screening and the assessment procedures were similar to those used in the AESOP study, a population based case control study conducted over 2 years in London, Nottingham and Bristol, aimed at comparing the incidence rates of psychotic disorders in three different centres (Kirkbride, Fearon et al. 2006).

The similarities in the methodology allowed me to make comparisons on the incidence rates of the overall psychotic disorders, of the specific psychotic disorders (schizophrenia, affective psychoses and other non-affective psychoses) and the risk in specific groups (e.g. in migrants and native-born Italians, in males versus females).

Clinical notes were checked in order to identify new admissions or new contacts for a first episode of any psychotic disorder within the catchment area.

When a patient satisfying the inclusion criteria was identified, he/she was invited to be enrolled in the study and after signing a consent form he/she went through the whole assessment; when the patient did not give the consent to be enrolled or he/she was unavailable to be asked for the consent, his/her main clinical and socio-demographic data were still recorded anonymously in a specific form according to the Italian law about the general authorization to process personal data for scientific research purposes (Gazzetta Ufficiale n° 72, 26 March 2012).

A retrospective analysis was run on clinical notes in all the services involved in the study in order to detect any missing patients.

If the patient was not available for the clinical assessment because he/she has been detected by the retrospective screening, the main socio-demographic and clinical information was collected using all available sources of data (clinical notes, computerized information systems, psychiatrists in charge of the subjects).

At the end of the study period, a leakage study was conducted in all the mental health services of the catchment area in order to detect all the cases of psychosis fulfilling the inclusion criteria, who could have been missed by the initial screening.

3.2.5 Case assessment

The following instruments were used for the assessment

1. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992) was used to interview patients who gave consent to go through the whole assessment. The SCAN Item Group Checklist (IGC) section was completed for those cases who refused to be interviewed or because of being detected retrospectively by the leakage study. All the raters completed a SCAN training.

Medical records were checked in detail to collect clinical and socio-demographic information for those who did not go through the whole assessment.

2. The Modified version of the Medical Research Council (MRC) socio-demographic scale (Mallett, Leff et al. 2002) was used to collect the main socio-demographic data on age, gender, ethnicity, place of birth, level of education, occupation.

The diagnosis of cases was made according to ICD-10 criteria for psychotic disorders using all the available information (SCAN, case notes, narrative history from any informants).

The diagnosis was confirmed case by case by consensus meetings among two psychiatrists and two trainees in psychiatry according to the Diagnostic Criteria for Research of the ICD-10 (DCR-10) which are designed specifically for research (World Health Organization, 1993). DCR-10 criteria for the psychotic disorders considered in this thesis are shown in **Appendix I**.

The ICD-10 diagnosis were divided as follows:

- All psychosis (F20-29, F30-33)
- Schizophrenia (F20)

- Other psychoses (F21-29): persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorder, other non-organic psychoses, unspecified non-organic psychotic disorders.
- Affective Psychoses included Mania, Bipolar Disorder, Depression with psychotic symptoms (F30-33).

When a patient did not want to take part in the study or he/she was identified retrospectively, the diagnosis was formulated on clinical notes and by the help of the psychiatrist in charge for that patient.

Migration status was defined as people who were born outside Italy. Ethnicity status was defined by self-ascription and by place of birth.

I identified a total of 204 psychosis cases. 183 were white Italians born and 21 were migrants. 68 cases accepted to be enrolled in the study and completed the whole assessment which is described in details in the following paragraphs.

3.3 Data management

3.3.1 The population at risk

Data on Palermo population were obtained through the 15° National Census 2011 available online (elaborated by the national Institute of Statistics, Istat). Most of the basic socio-demographic information (total population aged 18-65 years, split by age, sex, migration status and marital status) were downloaded as Excel datasets from the ISTAT website (<http://www.istat.it/it/istituto-nazionale-di-statistica>).

As in the AESOP study, the population at risk was broken down by 5-year age bands, except the first and the last age bands; the first age band was 18-24 and the last was 60-65.

When I standardized Palermo incidence rates to AESOP specific incidence rates, the latter have been recalculated using the same age bands.

The population at risk was further broken down by gender and migration status. This allowed me to calculate age and sex adjusted incidence rates and age, sex and migration adjusted incidence rate and incidence rate ratios. Population data of 2011 were multiplied by 3 to account for the 3 years study period to obtain the number of person-year at risk.

3.3.2 Numerator

Data of cases were built with the following variables:

- Age of contact with psychiatric services (age at onset)
- Gender
- Migrant status
- Diagnosis

3.3.3 Data manipulation

Age was converted into nine 5-year age bands for both cases and the population at risk. This artifice has been used in order to allow comparison between Palermo and UK incidence rates. Both numerator and denominator have been stratified by age, gender and migration status.

1. Both cases and the population at risk have been divided in a dichotomous category of migrants versus native-born Italians. I compared incidence rates between native-born Italians and migrants.
2. In the AESOP study, cases were divided according to ethnic group. In the Palermo sample, migrants were too few to group them for specific ethnicity. So I collapsed them into 4 large categories for descriptive purposes only: Italians, other Caucasians, Africans, Asians, even though I am aware that these groups, especially the last two categories, are heterogeneous in terms of ethnicity. For the incidence calculation however I only used the dichotomous variable native-born Italians versus migrants.

3.4 Statistical analysis for incidence

1. Descriptive epidemiology: I examined the age and sex structure of the population of cases and of the population at risk (denominator). I described the main socio-demographic characteristics of the sample of cases (age, gender, migration, level of education, relationship status, employment, living status).

2. I calculated crude incidence rates and their 95% confidence intervals for overall psychotic disorders and for each diagnostic category: schizophrenia (F20), affective psychoses including: mania, bipolar disorder and depressive psychosis (F30-33) and other psychosis (F21-29) by gender and by migration status. I calculated crude incidence rate ratios (IRR) and their 95% CI for males versus females and for migrants versus native-born Italians. Rates are presented per 100,000 persons/year.

3. I calculated age and sex specific incidence rates.

4. I applied Poisson regression models to obtain adjusted incidence rates and their 95% CI for age, sex and migration.

I used age as explanatory variable, because the incidence of psychotic disorders is influenced by age being higher among young people and in males (McGrath, Saha et al. 2004; Aleman, Kahn et al. 2003). I used gender as explanatory variable because males have been reported to have a higher risk of developing schizophrenia than females (McGrath, Saha et al. 2004; Aleman, Kahn et al. 2003).

I also used migration as an explanatory variable because it has been largely reported that being a migrant increases the risk of developing psychotic disorders (Cantor Grae and Selten, 2005).

5. I used Poisson regression to calculate adjusted incidence rate ratios and 95% confidence intervals to estimate the differences in incidence risk in different groups in the Palermo sample:

a. Males versus females (adjusting for age and migration): I applied the Likelihood Ratio Test (LRT) to test the interaction between age and migration. Since I did not find any significant interaction between age

bands and migration I used Poisson models assuming homogeneous IRR between migrants and native-born Italians for each age band.

- b. Migrants versus native-born Italians (adjusting for age and sex): I applied the Likelihood Ratio Test (LRT) to test the interaction between age and sex. Since I did not find any significant interaction between age bands and gender I used Poisson models without interaction assuming homogeneous IRR between males and females for each age band.

6. I calculated standardised incidence rates for overall psychotic disorders and for each diagnostic category, by age and gender and by age, gender and migration status, using indirect standardisation.

I used standardization to be able to compare the incidence rates found in Palermo to other populations, adjusting for possible confounders of the general population structure (age, gender, migration status). I used the indirect standardization instead of the direct standardization used in the AESOP study because of data availability.

I used AESOP data (Kirkbride, Fearon et al. 2006) as the standard population and I applied standard (AESOP) age-sex specific rates to Palermo population.

Palermo and AESOP surveillance periods were different (1997-1999 AESOP versus 2008-2011 Palermo), and this may have affected the comparison between sites; however UK incidence rates of psychoses were fairly stable over time (Kirkbride, Errazuriz et al., 2012) as discussed in more details in Chapter 6.

I obtained the standardized mortality ratio (SMR) given by the ratio of Palermo observed number of cases/expected number of cases in Palermo if the age–sex specific rates were the same as those of the standard population (Kirkwood and Sterne 2003). Age and sex adjusted rates for Palermo were obtained multiplying the SMR to the crude morbidity rate of the standard population.

I also standardized for migrant status. I applied standard (AESOP) migrant status (and age and sex) specific rates to Palermo population.

The definition of migration in Palermo was different to that in the AESOP study¹. Fearon and colleagues (Fearon, Kirkbride et. al, 2006) reported higher rates for all psychotic disorders and above all for schizophrenia and mania in ethnic minority groups (especially in Afro-Caribbeans and in Black African). In this thesis I considered “migrants”, all people who born outside Italy, and I compared them to people in the AESOP study who “born outside UK”. To avoid a bias based on the different migration history of the two populations I used an artifice: AESOP specific incidence rates have been re-calculated excluding second generation migrants that is people who born in UK but from migrant parents; Migration in Palermo is a recent phenomenon compared to UK, and the Palermo population is still quite homogenous; almost all the cases were born in Palermo from Italian parents. In UK population is made up by different ethnicities, and migrants do not represent a unique category (second generation migrants are included among “UK born”), so I decided to compare native-born Italians in Palermo with white British in AESOP excluding those belonging to ethnic minorities who are UK born to see whether there is a difference in terms of incidence. I also compared migrants in Palermo to non-UK born people in AESOP. I applied the AESOP age-sex rates excluding non-White British people from the sample in order to compare Palermo sample to native British population and non-British population of cases.

I did not compare incidence rates for different ethnic groups due to the small number of migrants in my sample.

In their paper Kirkbride and colleagues compared rates of psychosis in three centres (London, Nottingham and Bristol); however for this thesis I used AESOP data based on the London and Nottingham samples only. I excluded Bristol because data were not available for place of birth so I could not have identified migrants.

¹ In AESOP study the term migrants was used to indicate ethnic minorities who migrated to UK more recently. The term included also second- generation migrants who were born in UK. In this work instead, migrants refer to people who were born outside Italy.

The AESOP data set was manipulated to allow comparisons between the two samples. 19 AESOP cases from Nottingham and London have been dropped from the data set because place of birth was missing.

The age band 16-17 was also deleted to allow comparisons between AESOP and Palermo sample.

I excluded 23 AESOP cases with the diagnosis of substance-use psychosis because in Palermo I did not collect data on that.

I then excluded the non-White British population from the UK born people to allow a more sensible comparison to the Palermo sample. The total number of cases in AESOP used for the standardization was then 360.

For all of the reasons reported above, AESOP specific rates used for the standardization differ from those reported by Kirkbride and colleagues in their paper (Kirkbride, Fearon et al., 2006).

7. I compared Palermo incidence rates with those found in the AESOP study calculating SMR and its reciprocal and 95% CI.

The analyses were performed using Stata software (version 12).

3.5 Risk factors associated to psychosis: a case control comparison

After analyzing the incidence of psychotic disorders in my area, and after the incidence comparison to UK data, I was interested in investigating the distribution of environmental risk factors associated to the risk of developing psychosis in Palermo.

A different prevalence of risk factors potentially associated to the development of psychoses in my sample might explain, at least in part, the differences that have been found in the rates of psychoses between Palermo and UK.

I carried out a case control analysis in a subsample of 68 FEP patients identified for the incidence study and 74 healthy controls from the local population, aimed at:

- Comparing the prevalence of certain supposed environmental risk factors for psychosis in patients affected by a first episode of psychosis, and in healthy controls.
- Comparing the prevalence of environmental risk factors between the Palermo sample of cases and controls and similar samples of first episode psychotic patients recruited in London (GAP and AESOP study).

The case control design is an observational epidemiological study allowing to make comparisons of the prevalence of several exposures (putative risk factors) between a group of individuals who have the outcome of interest (in this case people affected by their first episode of psychosis) and a group of healthy people, with similar features to cases but without the disease of interest (controls). Case control studies are easier and less expensive and time consuming than prospective cohort studies, because the disease has already occurred.

They do not require large sample size unless the variable of exposure is very rare (Greenland, 2009) and have the advantage of allowing the study of several risk factors at the same time.

The case control study is prone to several biases, including the improper selection of either cases or controls (Parodi and Bottarelli, 2005).

The true measure of the association between an exposure and an outcome can be obtained ideally by measuring the association in the entire population; however, because it is not possible to study the entire population, the sampling of cases and controls must be representative of the exposure-outcome distributions in the overall population. The exposure distribution in the controls is used as an estimate of the exposure distribution in the overall population in order to compute the odds ratio as a measure of association (Boston University School of Public Health, 2012).

Selection bias may occur if the control group selected is not representative of the population the cases come from.

It may happen that the exposure under study may influence the selection of controls and this will lead to a bias in the estimate of the association between a certain risk factor and the outcome.

In case control studies, controls should represent the population at risk of the disease. More specifically, they should be individuals who, if they had experienced the disease outcome, would have been included as cases in the study (Kirkwood and Sterne, 2008).

Selection bias of cases may occur because of refusal, non-response, or agreement to participate that is related to the exposure and disease.

Another source of bias in case control studies is the recall bias, because the information about exposure to risk factors is collected retrospectively and people with the disease might be more likely to recall risk factors (Greenland, 2009).

Retrospective studies have more problems with data quality because they rely on memory and people with a condition will be more motivated to recall risk factors (also called recall bias).

3.5.1 The recruitment of cases and controls

3.5.1.1. The selection of cases

During the study period a total of 204 patients affected by a first episode of psychosis were identified for incidence calculation.

Only approximately 1/3 (68) of the sample of incident cases underwent the whole assessment. 136 patients were not involved in the study either because they refused to give the consent to be interviewed: 72 (53%) or because they had been screened and identified retrospectively: 64 (47%) were not available to be interviewed or they were not any longer in charge with psychiatric services.

68 patients who were actually in the care of psychiatric services accepted to be interviewed. They were asked to sign a consent form and they were enrolled in the study.

One issue is the selection bias of cases because it might be that those who accepted to be interviewed were more cooperative because of less

severe symptoms. I compared the 68 cases who have been recruited with 136 cases who were not enrolled because of refusal or because they were no longer in charge with the mental health services.

There were no significant differences in terms of gender, migration, ethnicity, level of education between the two groups. There was a difference in mean age at first contact: non-recruited cases were younger at their first contact.

Differences in diagnosis in the two groups were borderline. There was a higher proportion of people affected by schizophrenia in those who were recruited compared to the non recruited group.

3.5.1.2. The selection of controls

During the study period a healthy control group (n= 74) was recruited from the local population living in the same catchment area of cases. The research team and I tried to make any effort to collect a sample of controls that was representative of the general population at risk for the disease.

A quota sampling method was applied to select healthy controls. Palermo general population aged 18-65 was divided by age bands (18-34 and 35-65), gender, and migration status (native born people versus migrant). The control sample was selected according to the distribution of gender, age, and migration status observed in the population.

Therefore, the control sample was similar on a number of socio-demographic factors (age, gender, migrant status) to the population the cases come from.

We advertised the recruitment of controls through Internet, newspaper advertisements, leaflets placed in churches, gyms, private residences.

A selection bias could have occurred because people responding to advertisement might be more interested to go through a psychiatric or a psychological assessment because they suffer from any psychological disorder. A psychotic disorder in controls was excluded by administering the Psychosis Screening Questionnaire (Bebbington and Nayani 1995).

Four people were excluded because of screening positive to the questionnaire.

The leaflet for the advertisement did not mention cannabis, other drug consumption, or any other risk factor to minimize the effect of selection bias driven by the exposure.

As mentioned previously, another bias in case control studies may be recall bias. However this is a first episode study so that the detrimental effect of medication and the impact of cognitive impairment on the ability to recall may be reduced.

3.5.2 The assessment of cases and controls

Beside data on age, gender, the basic socio-demographic data (level of education, occupational and social status, living status migration status) acquired from the incidence part of the study, the main risk factors investigated in this thesis in the case control analyses are:

- Family history of psychiatric disorders in the first degree relatives
- Cannabis and other illicit drug consumption
- Traumatic experiences in childhood and early adolescence (such as physical or sexual abuse, separation from parents for more than six months, death of one parent)
- Adult adversities.

All of these variables have been associated to an increased risk of developing a psychotic disorder even though the results of different studies are not univocal (see the introduction chapter for further details).

Data on family history of any psychiatric disorders and psychosis in first degree relatives of patients and healthy controls were collected by the Family Interview for Genetic study (FIGS), an interview designed to gain information about the presence of a psychiatric disorder in first degree relatives of the patients (depression, mania, alcohol and other drug abuse, psychosis, paranoid/schizoid/schizotypal personality disorder) (NIHM Genetic Initiative, 1992).

Detailed data on cannabis and other illicit drugs consumption were collected by the Cannabis Experience Questionnaire modified version, CEQmv, (Di Forti, Morgan et al. 2009) (see Appendix III) to investigate qualitative and quantitative information on cannabis (age at first use, frequency, duration of use in years, current or past use) and other substances of abuse consumption.

Positive and Negative Syndrome Scale (PANSS) was used to evaluate symptom severity (Kay, Fiszbein 1987).

Childhood traumatic experiences, loss or separation from parents, physical and sexual abuse before age of 17 were investigated by the Childhood Experience of Care and Abuse (CECA) Questionnaire modified version (Bifulco et al., 2005); adult adversities (bullying, violence at home, being victim of serious injury, illness or assault), were assessed by the Brief Life Events schedule adapted from Bebbington et al. (2004).

CECA and Brief Life Events schedule were included in the assessment of the Modified version of the Medical Research Council (MRC) socio-demographic scale (see Appendix IV).

A more detailed description of the instruments for the assessment will follow in the next paragraph.

3.5.2.1 The assessment of cases: measurements and variables analysed in the study

Cases were assessed by the following tools:

1) Socio-demographic data (age; gender; ethnicity; level of education and employment status) on cases and controls were collected using a modified version of the **MRC Sociodemographic Schedule** (Mallett, Leff et al. 2002). Some variables such as ethnicity and level of education have been modified according to the Italian context.

The relevant information for this thesis were: age at first contact with psychiatric services, gender, age, ethnicity, place of birth (used to define migration status), employment status, relationship status and living

status at the time of the assessment, level of education. The same MRC tool was also administered to controls.

- Age indicated the age at first contact with psychiatric services; in controls it indicated the age at the time of the assessment.
- Ethnicity has been collapsed into a dichotomous variable: Caucasian, not Caucasian.
- Place of birth was considered to create a dichotomous variable: Italy or not Italy born. People who were not Italy born were defined as “migrant”.
- Living status included several categories (living alone, living with partner/spouse, living with children etc. see appendix for details); to simplify the analyses a dichotomous category was created: living alone/living with someone.
- Employment status was descriptively differentiated in employed, unemployed, student, retired. It was collapsed in a dichotomous category: employed/unemployed.
- Relationship status was differentiated in two groups: single, separated, divorced/in a stable relationship.
- Level of education was defined into the following categories (the UK categories of the tool were modified according to the differences in the Italian education system): no qualification, primary school, junior high, diploma (secondary school degree), University. To simplify the analyses, mean age of leaving education was considered to compare cases and controls.

2) The Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992) was used to assess psychopathology.

This is a set of instruments aimed at assessing and classifying the psychopathology of the major psychiatric syndromes. It includes the Present State Examination (PSE 10) to evaluate symptoms present for the month before assessment.

Information on those subjects who could not be interviewed was derived by case-notes, employing the section, Item Group Checklist (IGC) of the SCAN.

The diagnosis according to the ICD-10 criteria (F20-29, F30-F33) was established by consensus among two adult psychiatrists and two trainees (psychiatrists or psychologists) who performed the interview of the patient.

3) The Family Interview for Genetic Studies (FIGS; NIMH Genetics Initiative, 1992) was used to gather information about the history of psychiatric disorders in first-degree relatives (parents, children) of cases and healthy controls.

This tool requires one to draw a pedigree diagram. General screening questions are asked about the relatives in the pedigree to detect mental health problems in subjects' relatives. Then the Face Sheet is used to or any affected relatives about whom the informant can provide information <https://www.nimhgenetics.org/interviews/figs>.

In the analysis I chose to consider psychosis, mood disorders, mania.

The variables were grouped into:

- A dichotomous variable indicating the presence or the absence of any psychiatric disorder (psychosis, mood disorder, mania) in one of the first-degree relatives.
- A dichotomous variable indicating the presence or the absence of any psychotic disorder in one of the first-degree relatives.

4) Cannabis Experience Questionnaire modified version CEQmv, (Di Forti, Morgan et al. 2009). This is a questionnaire aimed at gathering information on pattern of cannabis consumption. The following variable were explored:

- Age at first cannabis use

- Use before and after 15 years: a dichotomous variable has been created to split subjects into two groups: (1: those who started smoking before 15 years, 0: those who did not).
- Lifetime cannabis consumption: a dichotomous variable (yes/no) exploring whether the subject has ever used cannabis at least once during life.
- Current cannabis consumption: a dichotomous variable (yes/no) exploring whether the subject is a current cannabis user. Current cannabis use is defined as cannabis consumption within the four weeks before the assessment.
- Frequency of use includes several categories (never used, only once or twice, a few times each year, a few times each month, once a week, more than once a week, everyday). For power reasons frequency has been collapsed into a dichotomous variable: daily cannabis consumption/cannabis consumption less than everyday. Frequency has been also collapsed into another dichotomous variable taking into account the total number the subject has smoked cannabis (<50 times, >50 and over 200 times)
- Mean duration of cannabis use: a dichotomous variable has been created; 5 or less than five years/more than five years of cannabis use.
- Other drug consumption: collapsed into a dichotomous variable exploring lifetime consumption (yes/no) of other drugs (including all illicit drugs), stimulants, tobacco, alcohol.

5) Childhood Experience of Care and Abuse Questionnaire (CECA Q) (Bifulco et al. 2005). A short version of the questionnaire was included in the assessment. This questionnaire is aimed at assessing early adverse experiences prior of age 17. In this thesis I considered four early adversities: parental loss because of death, parental separation, physical abuse, sexual abuse.

- Parental loss was categorised into a dichotomous variable: presence

or absence of an experience of losing any parent because of death before age 17.

- The presence or an experience of separation from mother or father (not living with one of the parents) for a period of at least six months is reported in a dichotomous variable (yes/no).
- The presence of physical abuse defined as the repeated exposure to physical violence from mother or father before age 17. It was analysed as a dichotomous variable (yes/no). Physical abuse was scored as present (yes) only when the physical punishment was severe (being hit repeatedly with an implement, being punched, kicked, or burnt, being injured or bruised).
- The presence of sexual abuse was reported if the abuse was severe according to the CECA cut-off points (Bifulco, 2005). It was analysed as a dichotomous variable (yes/no).

6) **Brief Life Events Schedule modified version** (adapted from Bebbington et al. 2004) was included. A list of ten victimization experiences (serious injury or assault, bullying, violence at work, violence at home, sexual abuse, being expelled from school, running away from home, being homeless, taken into local authority care, time in children's institution) was shown to the participant and he/she was asked if he/she had experienced any of these victimization experiences at any time during his/her life. A dichotomous variable (yes/no) was created for each of these experiences.

7) **Positive and Negative Syndromes Scale** (Kay, 1987). This is a 30-item rating scale providing quantitative information on positive and negative symptoms and global psychopathology. Each item is rated on a 7-point (1–7) scale; items are grouped into 3 subscales: positive symptoms, negative symptoms and general psychopathology.

8) Nottingham Onset Schedule (NOS) (Singh et al., 2005). This is a short interview to measure onset in psychosis. Onset is defined as the time between the first reported/observed change in mental state/behaviour to the development of psychotic symptoms. It provides a measure of the duration of untreated psychosis (DUP). In this study DUP was defined as the period in weeks from the date of the first appearance of clinically relevant psychotic symptoms to the date of first contact with mental health services for psychosis (Morgan et al., 2006; Singh et al., 2005). Since some cases reported long DUP, weeks were converted into months to ease the analyses.

PANNS and NOS have been reported just for descriptive purposes since their data has not been entered in the analysis.

3.5.2.2 The assessment of controls: measurements and variables analysed in the study

Controls inclusion criteria were:

- Age 18 to 65
- Resident in the catchment area
- Absence of learning disabilities
- Absence of previous psychotic symptoms.

They were assessed by the **Psychosis Screening Questionnaire** (PSQ) (Bebbington and Nayani 1995) (see appendix V) to exclude the presence of a psychotic disorder. The questionnaire includes questions to screen symptoms of hypomania, thought interference, persecution, perceptual abnormalities, strange experiences and hallucinosis together with a question on a previous treatment for a psychiatric problem. People were excluded if they had previous treatment for psychosis or if they answered positively to at least two of the questions of each symptom.

Four people were excluded because of screening positive on the PSQ.

They were administered the same questionnaires and schedules as cases except for SCAN, NOS, and PANSS.

Controls exclusion criteria were:

- Age under 18 or over 64
- Current or past psychotic disorder (or treatment with antipsychotic medication);
- IQ<70.

3.5.3 Justification of sample size: power calculation for case-control study

I used the Epi-Info program to calculate the sample size needed to achieve a study power of 80% at a 5% significance level (equivalent to a 95% CI) with an equal number of cases and controls.

Epi-Info requires 3 information to do the power calculation:

- a. desired level of power (80%) and level of significance (5%)
- b. the expected prevalence of exposure to the risk factor of interest in the controls
- c. the expected magnitude of the effect (OR) of the risk factor selected.

The Epi-Info calculation indicated that to obtain a power of 80%, with a level of significance of 5%, assuming a prevalence of exposure to cannabis use of 22.4% in the control group (taking into account national data on the population prevalence of cannabis consumption), I need a sample of 122 people (61 cases and 61 controls), to detect a moderate main effect (Odds Ratio=3).

This thesis also takes into account the exposure to other environmental risk factors such as childhood adverse experiences and adult adversities. It is not easy to estimate the prevalence of all these adverse events in the general population. However I choose sexual abuse that is a quite rare event in order to calculate the power I needed to detect a moderate effect of abuse on the risk of developing psychosis. To calculate power for sexual abuse, I used the one-sided binomial test (Chow, Shao et al. 2003). It indicated that to obtain a power of 80%, with a level of significance of 5%, assuming a prevalence of exposure to

sexual abuse of 10% in the general population (taking into account European data on the population prevalence of sexual abuse, World Report on violence and health, WHO 2002) I need a sample of 110 subjects (55 cases and 55 controls), to detect a modest effect (Odds Ratio=2).

3.5.4 Statistical analysis for the case control study

The statistical methods commonly used for case control studies are odds ratio (OR) and chi square test. Logistic regression is used to adjust for confounding variables. For rare diseases the odds ratio (OR) is equal to risk ratio and rate ratio.

- I compared the prevalence of risk factors between cases and controls in the Palermo sample using as appropriate chi square test and Fisher exact test.
- I calculated unadjusted odds ratio for the main exposures (cannabis and other illicit drug consumption, childhood traumatic experiences, adult adverse events, family history of psychiatric disorders in first degree relatives).
- I calculated adjusted OR applying, whenever it was possible, stepwise logistic regression to adjust for the main confounders (age, sex, level of education, psychiatric disorders in first degree relatives, employment).
- I applied t test, Wilcoxon, Welch test and ANOVA to analyze quantitative variables in cases and controls.

3.6 Software

Microsoft Excel was used to obtain and manipulate the denominator data for the Palermo and the AESOP population (the population standard).

SPSS (version 20) was used to build both individual datasets including all the variables of interest for the case control analyses and collapsed datasets with age and sex bands, migration, diagnosis and their corresponding denominator to perform incidence analyses.

I converted the final datasets into Stata by STAT TRANSFER version 8. Stata version 12 has been used for descriptive and analytical analysis.

3.7 Ethics

The study was approved by the Ethical Committee of the Palermo University Medical School in 2008 and the data collection in the mental health services has been authorized by the Department of Mental Health of Palermo which is the coordinator of all the psychiatric services in the catchment area involved in the study.

As reported in the previous paragraph when a patient was not available to be asked the consent, his/her main clinical and socio-demographic data were recorded anonymously according to the Italian law about the general authorization to process personal data for scientific research purposes (Gazzetta Ufficiale n° 72, 26 March 2012) which allows the collection of anonymous epidemiological data even without a specific consent given by the subject. This ensured the possibility to collect all data needed to estimate the incidence of psychosis in Palermo.

3.8 Statement of contribution to the investigations

My work has been inspired and guided by my supervisors.

Prof. Sir Robin Murray, Prof. Paul Fearon and James Kirkbride have helped me in discussing several methodological issues. Prof. Daniele La Barbera helped me in organizing the research study.

I coordinated the Sicilian Genetic and Psychosis study (S-GAP) research team of psychologists and psychiatrists in training who performed the screening in the mental health services together with me. I was responsible for the ethical approval application and I contributed to defining the battery of assessments used in the project. I coordinated the screening procedure of people referred to the mental health services of Palermo; I defined the method to collect any missing data and the leakage study.

I attended a training course to administer the SCAN interview and I carried out the clinical assessment on a large proportion of the FEP recruited.

I have been actively involved in the recruitment of both cases and controls and in the participants' assessment and in the retrospective study on clinical notes in order to identify any missing case of psychosis. I organised the project's initial database (SPSS 20) and I built the variables relevant to my thesis.

I could not have collected all the incidence and case controls data without the efforts of the research team I coordinated.

Chapter 4

Incidence of Psychotic Disorders in Palermo

4.1 Introduction

In this chapter I will provide data on the incidence of psychotic disorders in Palermo. I will describe in detail the population denominator and the catchment area. I will report incidence rates for overall psychotic disorders by diagnostic categories and by gender. I will report both crude and standardized rates. I will explore whether there is a difference in incidence rates by migrant status as it has been reported that migration is one of the risk factors for psychosis. I will then compare Palermo incidence data with AESOP incidence rates in UK and discuss the main possible explanations for any rate differences found.

4.2 Denominator data

Table 2 reports the population of Palermo residents aged 18-65 years in 2011 according to the 2011 census (Istat, 2012) and split into native-born Italians and migrants. The total population was 412,771 people. Males were 199,952, females were 212,819. In this thesis I define migrants as all the people who originally were born outside Italy. In 2011 migrants represented 4.2% of the total population (SISTAN, 2012).

I considered the population in 2011 when there was a new population census, in order to use the most accurate data for the denominator. I then multiplied by 3 to obtain the number of persons at risk in the period of three years giving a total population at risk of 1,283,739 persons. The Palermo population aged 18-65 years and split by age-bands, gender and migrant status is shown in **Appendix section (II)**.

Table 2: people resident in Palermo in 2011 aged 18 to 65 years according to the census (Istat, 2012). This population has been split into two categories (native-born Italians and migrants) providing the denominator for the incidence rate calculation.

	Total (M +F)	Males	Females
Native-born Italians	412,771	199,952	212,819
Migrants	15,142	7600	7542
Total residents (Native-born Italians + migrants)	427,913	207,552	220,361

4.3 Numerator data

Two hundred and four patients with their first episode of psychosis (FEP) met the inclusion criteria over the study period. 68 (33.3%) FEP were assessed by face to face interviews. 136 (66.7%) cases were not assessed in a face to face interview: 72 (35.3%) of the 204 cases, refused to be interviewed and 64 (31.3%) were identified by the leakage study. The main reason for refusing to be enrolled was lack of interest and motivation in the research and the fear of being stigmatized.

The total sample for analysis therefore comprised 126 males and 78 females. As described in previous first episode psychosis studies (Kirkbride, Fearon et al., 2006), there were more males (61.8%), than females (38.2%). 183 (89.7%) cases were native Italians and 21 were migrants² (10.3%).

Table 3: distribution of cases by gender and migration status.

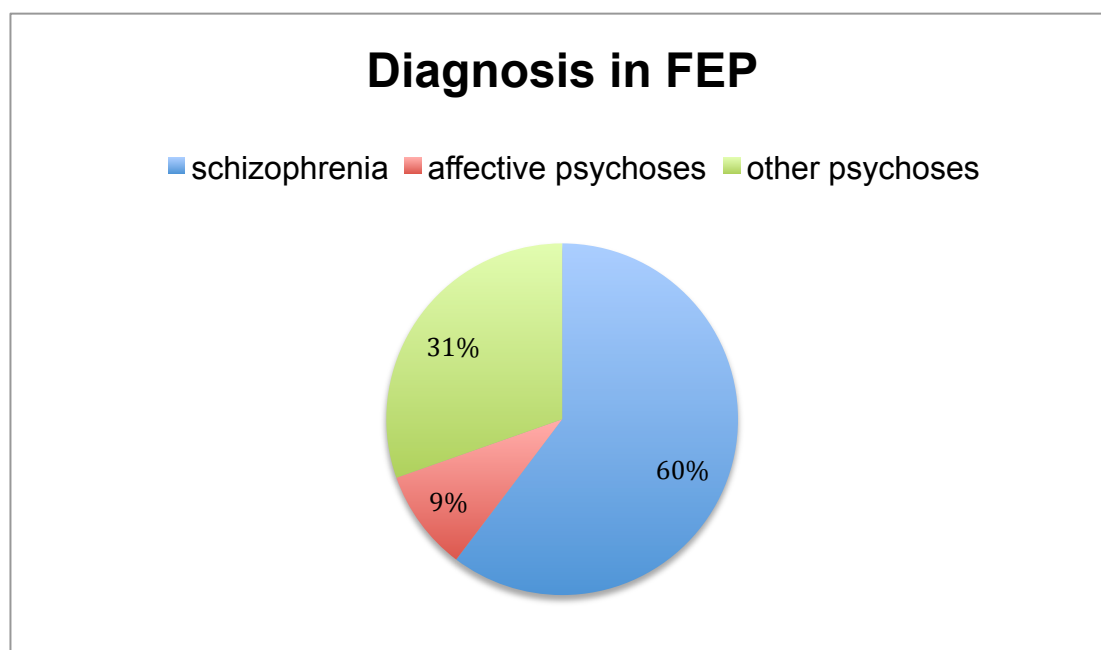
Palermo	Total, (n %)	Males n, (%)	Females n, (%)
Cases	204	126 (61.8)	78 (38.2)
Native-born Italians	189 (89.7)	112 (88.9)	71 (91)
Migrants	21 (10.3)	14 (11.1)	7 (9)

² In this thesis the term migrants refer to people who born outside Italy as explained in the previous chapter (methods).

4.3.1 Diagnosis

Fig 3 shows the distribution of the diagnoses in cases. 123 (60.3%) subjects met ICD-10 criteria for the diagnosis of F20 schizophrenia, 19 (9.3%) for F30-33 affective psychoses, 62 (30.4%) for other non- affective psychoses F21-29.

Figure 3: the ICD-10 diagnosis distribution among the 204 cases of psychoses.

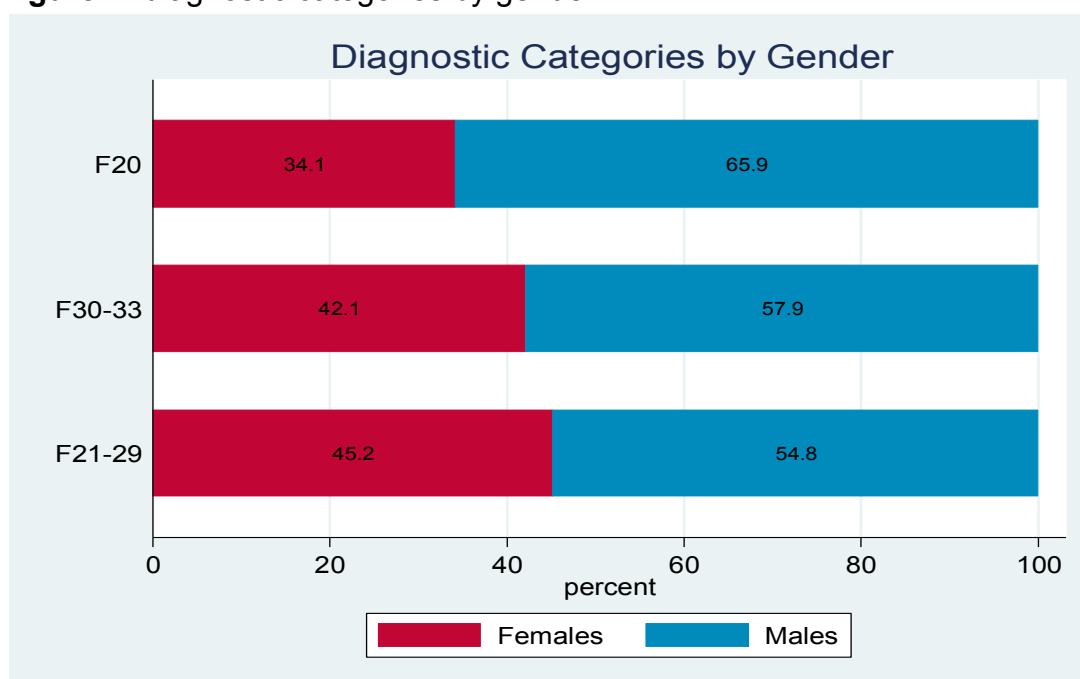


The affective psychosis category was composed of 12 (63.1%) people affected by mania or bipolar disorder and 7 (36.9%) people by depression with psychotic symptoms.

123 subjects were diagnosed with schizophrenia F20; 81 (65.9%) were males and 42 (34.2%) females. 19 patients received the diagnosis of affective psychosis F30-33, 11 (57.9%) were males and 8 (42.1%) females. 62 had other non-affective psychosis F21-29, 34 (54.8%) were males and 28 (45.2%) were females. Diagnoses are displayed split by gender in **Table 4** and in **Fig 4**.

Table 4: distribution of ICD-10 Diagnostic Categories of the cases by gender

Sex	F20 (n, %)	F30-33 (n, %)	F21-29 (n, %)	All psychosis (n, %)
M	81 (65.8)	11 (57.9)	34 (54.8)	126 (61.8)
F	42 (34.2)	8 (42.1)	28 (45.2)	78 (38.2)
Total	123 (100)	19 (100)	62 (100)	204 (100)

Figure 4: diagnostic categories by gender

If we consider 2 categories: affective and non-affective psychoses, 19 (9.3%) of subjects had a diagnosis of affective psychosis (mania or depressive psychosis), 185 (90.7%) a diagnosis of non-affective psychosis (schizophrenia, schizoaffective, other psychosis).

4.3.2 Age of first contact with mental health services

The median age of first contact with psychiatric services for all psychoses was 28 years (IQR 16); mean and median age at first presentation for each diagnostic category is shown in **Table 5**. Mean and median age is different because of the asymmetric distribution of age. I used Kruskal Wallis to compare distribution of age of different diagnostic categories because of the asymmetric distribution.

There was a difference in the distribution of age at first presentation across diagnostic categories ($\chi^2=12.5$, $df=2$, $p\text{-value}=0.002$, Kruskal Wallis) as shown in **Fig. 5**.

There was not any difference in median age at first presentation between schizophrenia and affective psychoses ($\chi^2=0.10$, $df=1$, $p\text{-value}=0.714$, Kruskal Wallis) while the difference between median age at first presentation of schizophrenia and other non-affective psychoses was significant ($\chi^2=12.1$, $df=1$, $p<0.001$, Kruskal Wallis). People diagnosed with other non-affective psychotic disorders (F21-29) tended to develop the disorder later than those affected by schizophrenia. This finding might be explained in part at least by the diagnostic category of F21-29 that includes disorders such delusional and schizoaffective disorders which tend to have their onset later in life.

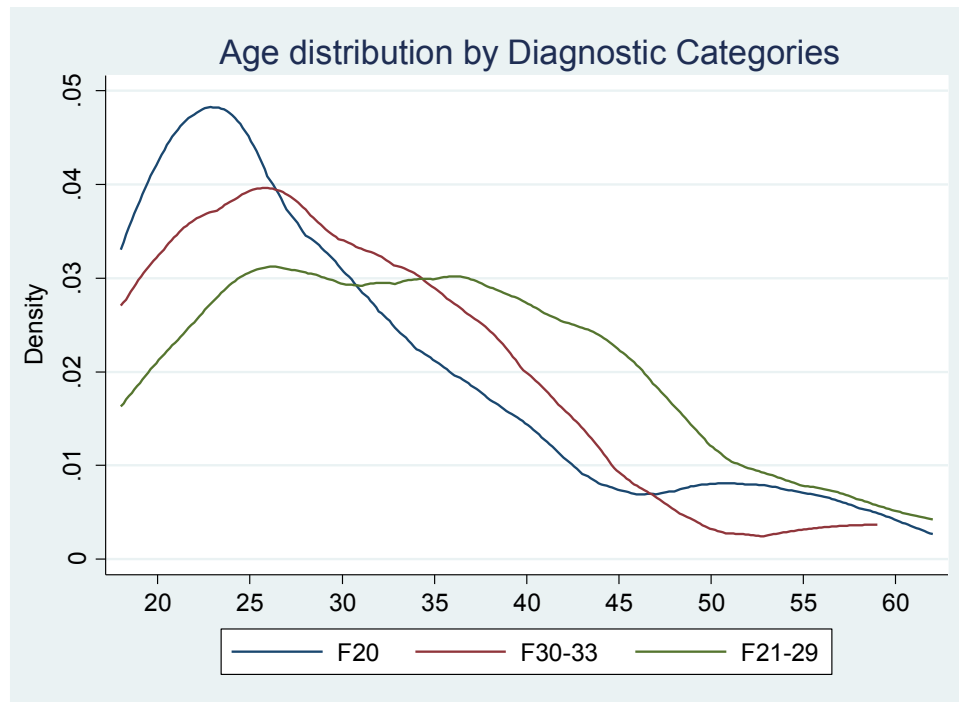
Table 5: mean and median age at first presentation by diagnostic category.

Diagnosis	Mean age of first contact (s.d.)*	Median age of first contact (IQR)**
All psychoses F20-33	31.2 (11.2)	28 (16)
Schizophrenia F20	29.6 (10.9)	26 (9)
Affective Psychosis F30-33	29.8 (10.3)	29 (13)
Other psychosis F21-29	34.9 (11.2)	33 (16)

*s.d: standard deviation.

** IQR: Intequartile Range

Figure 5: age distribution by diagnostic category.

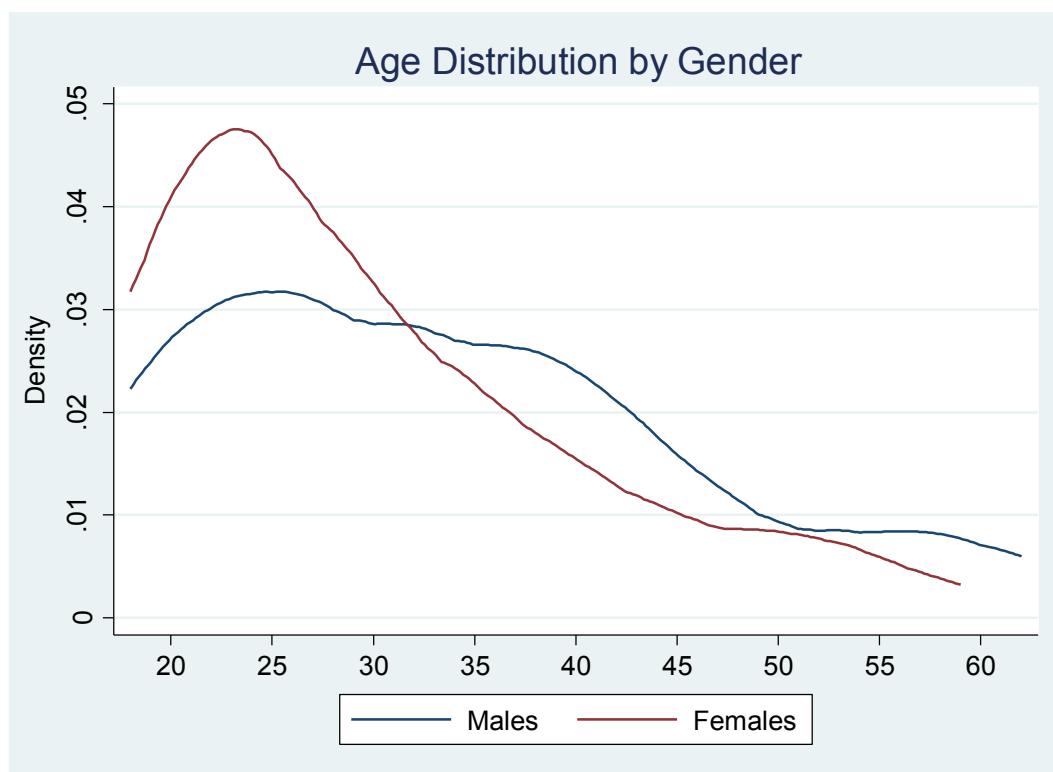


I then compared median age at first presentation by gender for overall psychotic disorders and by each diagnostic category.

Median age at first presentation for overall psychoses was significantly higher in females 32.5 (IQR:16) than males 26.5 (IQR:13) ($z=2.3$, $p\text{-value}=0.020$, Wilcoxon test) as shown in **Fig 6**.

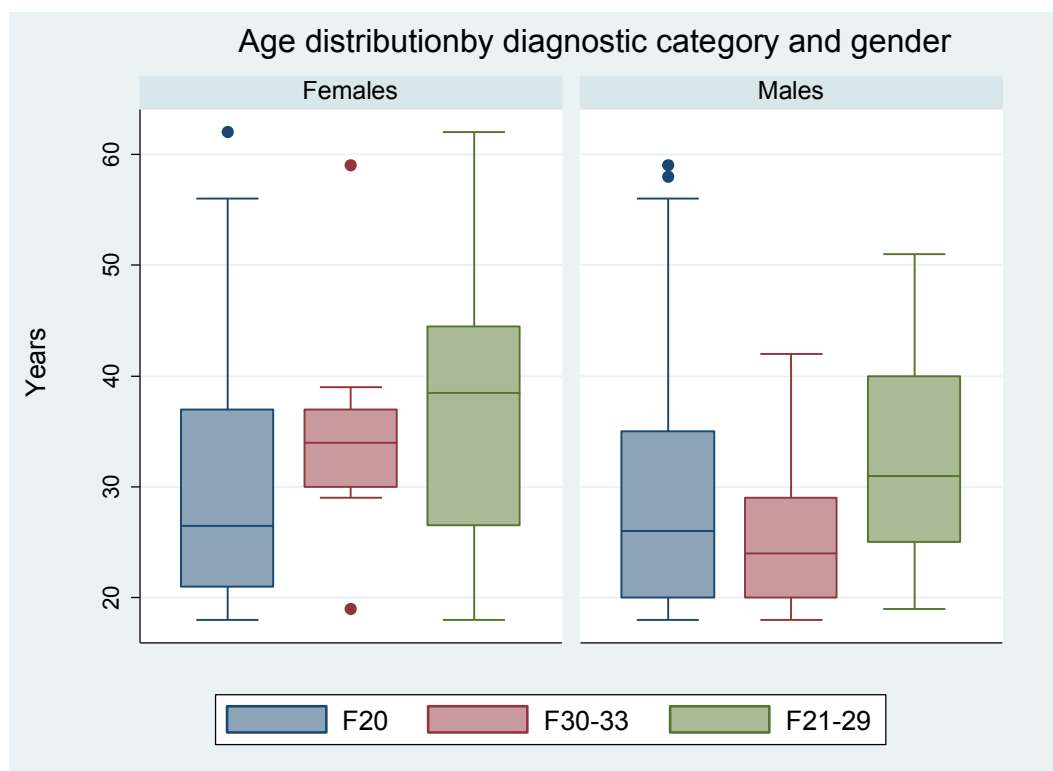
This result overlaps with the AESOP study in which the median age at first presentation was 27 years in men (IQR: 22-34) and 30 years in women (IQR: 24-39).

Figure 6: age distribution by gender: females are older than males at their psychotic onset when considering overall psychotic disorders.



Age distribution by diagnostic category and gender is displayed in **Fig 7**.

Figure 7: age distribution by diagnostic category and gender.



When I split cases into the two categories: affective psychoses (mania and depression with psychotic features) and non-affective psychoses (schizophrenia and other psychoses), I did not find any significant difference in the median age at first presentation ($z=0.5$, $p\text{-value}=0.641$, Wilcoxon test) as shown in **Fig 8**.

Figure 8: age distribution in affective and non-affective psychoses.

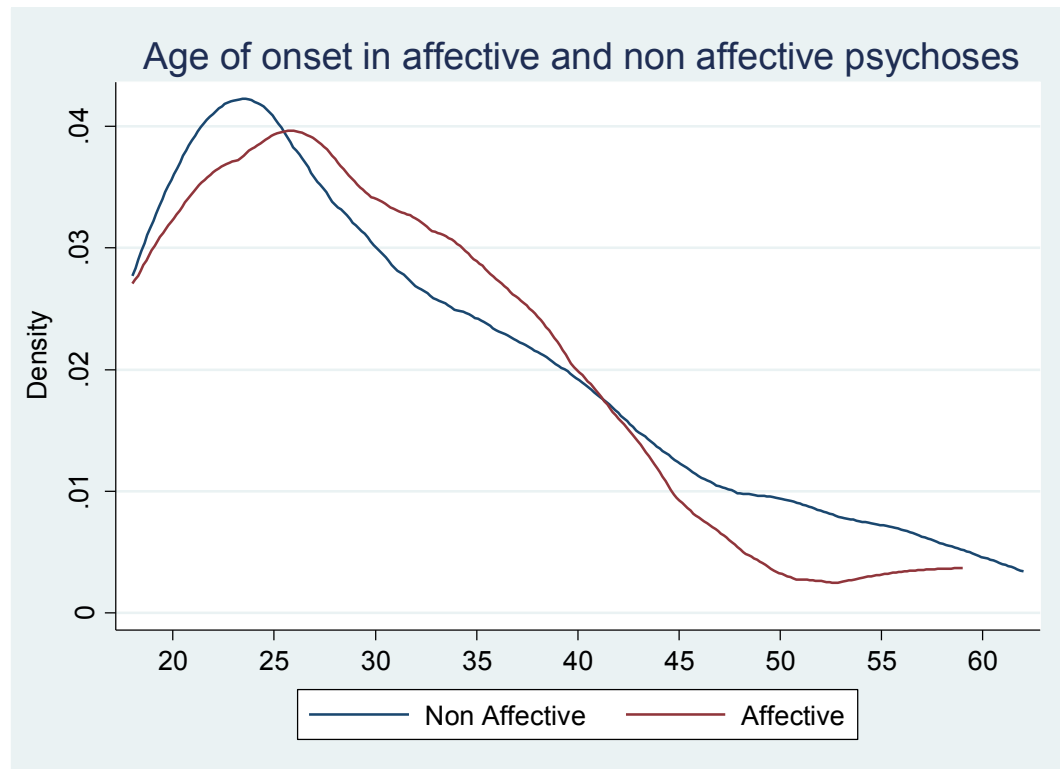


Table 6 summarizes mean and median age at first presentation by gender and by diagnostic category.

Median age was lower than mean age because of the positively skewed age distribution of psychoses. I applied Wilcoxon test to compare median age in males and females by diagnostic category because of the non-normal distribution of age at first presentation.

I found a significant difference between median age at first presentation by gender for all psychoses ($z=2.3$, $p\text{-value}=0.020$, Wilcoxon test), but when I repeated the analyses by each diagnostic category, the differences in the median age at first contact by gender became non significant.

Table 6: mean and median age of first contact of service (years) in cases for different diagnostic categories. p values refer to median age at first contact.

Diagnostic category		Total	Male	Female	p value*
All psychoses					
Mean (s.d)		31.2 (11.2)	29.7 (10.3)	33.7 (12.2)	
Median (IQR)		28 (16)	26.5 (13)	32.5 (16)	0.020
F20 Schizophrenia					
Mean (s.d)		29.6 (10.9)	29 (10.7)	30.6 (11.3)	
Median (IQR)		26 (14)	26 (15)	26.5 (16)	0.393
F30-33 affective psychoses					
Mean (s.d)		29.8 (10.3)	26 (8)	35 (11.3)	
Median (IQR)		29 (13)	24 (9)	34 (7)	0.069
F21-29	Other non-affective psychoses				
Mean (s.d)		34.9 (11.2)	32.4 (9.2)	38 (12.7)	
Median (IQR)		33 (16)	31 (15)	38.5 (18)	0.093

*p values from Wilcoxon test

4.3.3 Socio demographic characteristics of the sample

Socio-demographic data on level of education, relationship and employment status, living status (with someone or alone), migration are summarized in **Table 7**.

Most of the patients had a diploma (42.7%) or a junior high certificate (36.7%).

Patients were mostly single or separated (72.7%), and unemployed (54.1%). 94.5% of the patients lived with someone in the household and only the 5.5% lived by themselves.

This may represent a feature of Italian family structure which might differ from other countries, and may have implications for the course and the outcome of patients affected by a psychotic disorder.

Table 7: socio-demographic features of 204 cases.

Cases	n (%)
Level of education	
No qualification	2 (1.3)
Primary school	16 (10.7)
Junior high	55 (36.7)
Diploma	64 (42.7)
University	13 (8.7)
No details	54
Relationship status	
Single/separated/divorced	125 (72.7)
Steady relationship/marriage	47 (27.3)
No details	32
Employment status	
Unemployed	92 (54.1)
Employed	52 (30.6)
Student	24 (14.1)
Retired	2 (1.2)
No details	34
Living with someone	
Yes	139 (94.6)
No	8 (5.4)
No details	57
Migrant	
Yes	21 (10.3)
No	183 (89.7)

4.4. Incidence rates of psychotic disorders in Palermo

4.4.1 Specific incidence rates by age bands

Fig 9 displays specific rates and their 95% CI of all psychotic disorders by age bands. The highest incidence rates for all psychotic disorder fall in the age bands of 18-24 and 25-29 years.

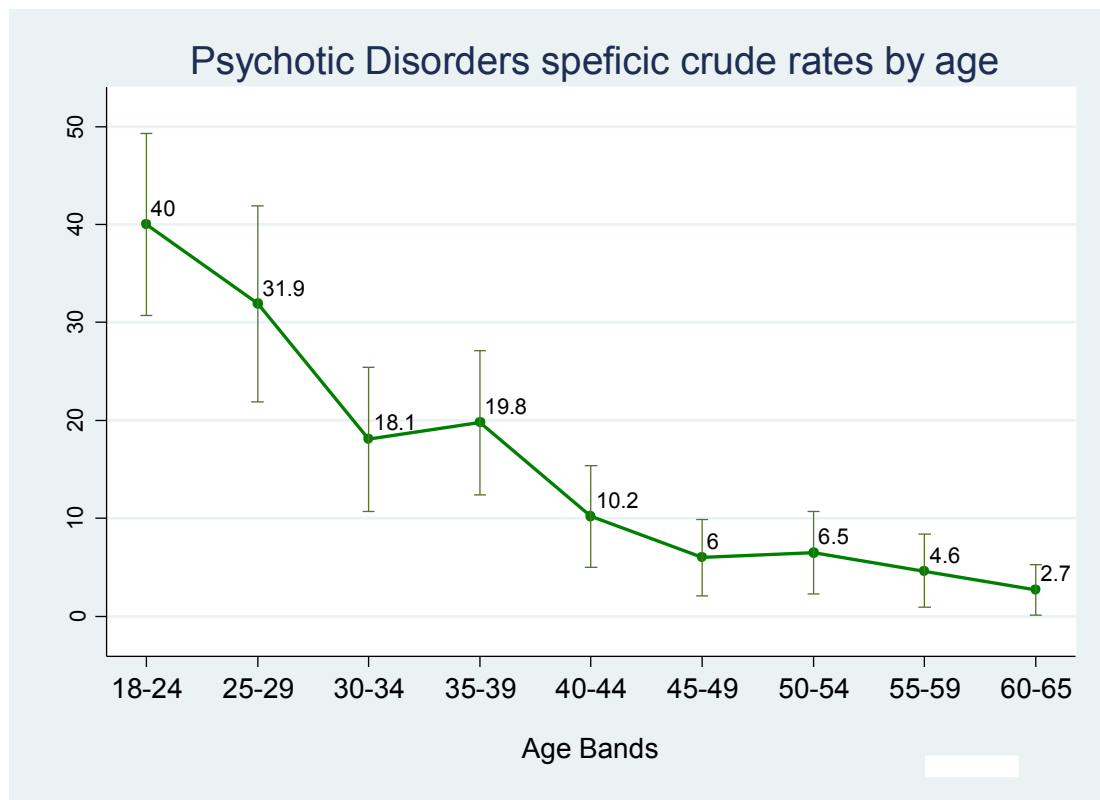


Figure 9: specific incidence rates and their 95% CI for overall psychotic disorders by age-bands.

Age and gender specific incidence rates for all psychoses are shown in **Fig 10**.

Males show higher specific rates than females for all psychoses till 30-34 years; then at 35-39 the rates tend to overlap.

The same distribution of age has been found in the AESOP study as is shown in the **Fig 11** (Kirkbride, Fearon et al. 2006) where the curves overlap around age 35-39.

Figure 10: specific incidence rates and their 95% CI for overall psychotic disorders by age-bands and gender.

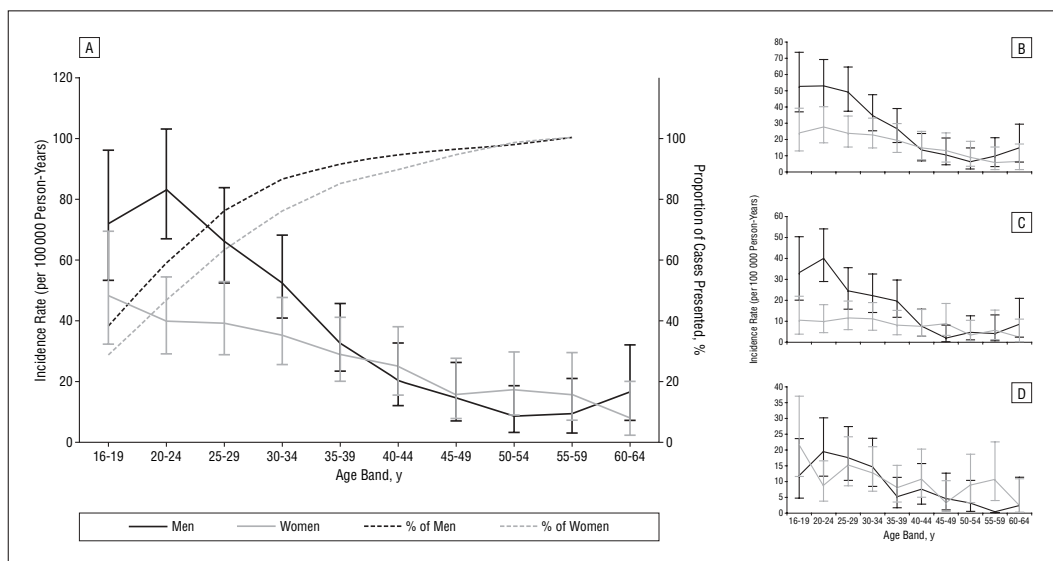
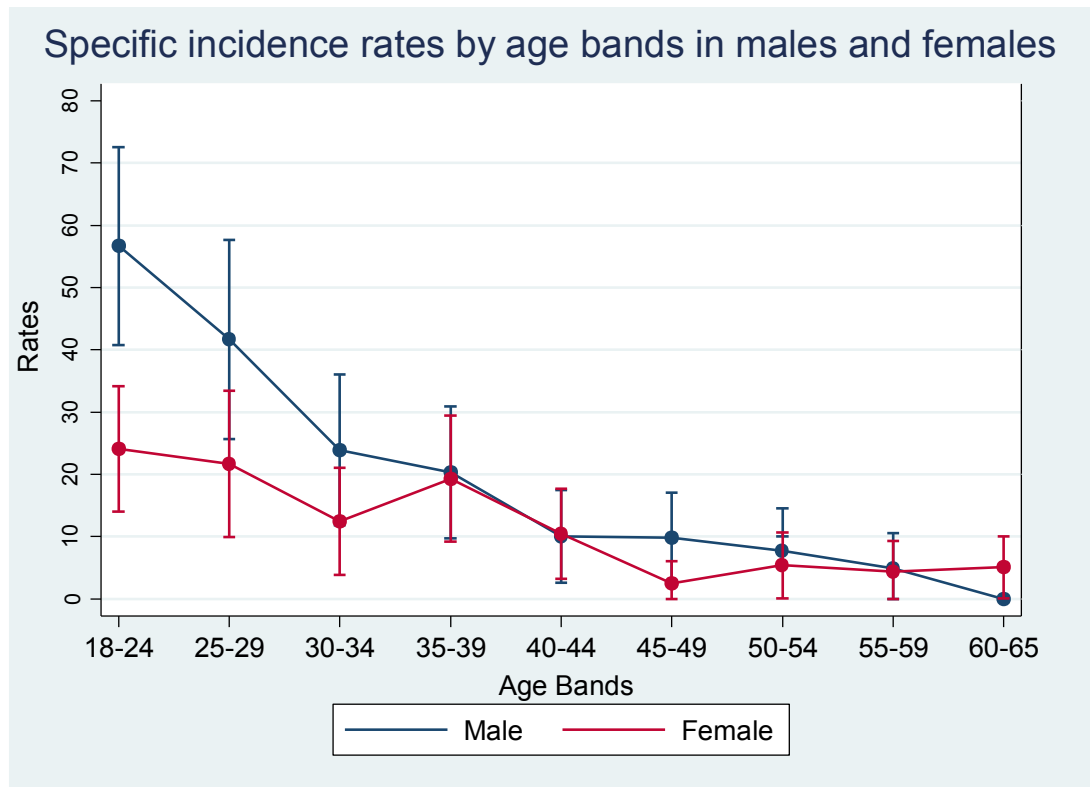
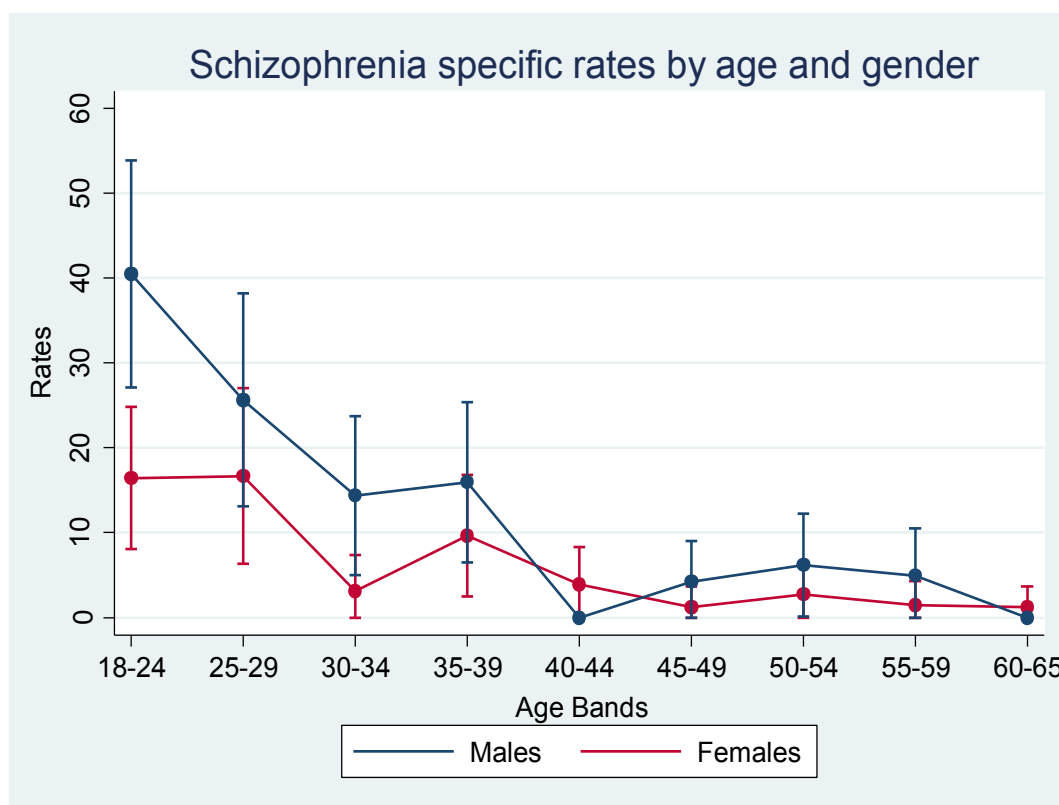


Figure 1. Cumulative proportion of all psychoses by age and sex and age-specific incidence rates of selected psychoses by sex. A, All psychoses. B, Nonaffective psychoses. C, Schizophrenia. D, Affective disorders.

Figure 11: this picture from Kirkbride, Fearon et al. 2006, shows in graph A the age and sex specific incidence rates of overall psychotic disorders in the AESOP study.

Specific incidence rates for schizophrenia by age bands and gender have been calculated and displayed in **Fig 12**.

Figure 12: schizophrenia specific incidence rates by age bands and gender with their 95% CI.



When considering the distribution of age by gender for schizophrenia the rates tend to overlap both in Palermo **Fig 12** and in AESOP **Fig. 11** (graph C) at the age of 40-44.

4.4.2 Incidence rates by diagnostic category and gender

Table 8 shows incidence rates for all psychoses and by diagnostic categories.

Crude rates are displayed per 100,000 person years, (total and by gender).

According to the literature, the incidence of schizophrenia is higher in young people and in males. I adjusted incidence rates by age and migration applying Poisson regression. I calculated incidence rate ratios

(IRR) and their 95% CI for each diagnostic category for males and females to detect whether there was a difference in risk of developing any psychotic disorders between males and females.

Before adjusting incidence rates by age and migration I tested the absence of an interaction between age and migration by the likelihood ratio test (LRT), assuming that the rates are homogeneous among native-born Italians and migrants by each age band.

Table 8: crude incidence rates (total and by gender) for overall psychoses and for each diagnostic category (rates are displayed per 100,000 persons per year). Crude and adjusted incidence rate ratio (IRR) with their 95% CI for males and females.

Incidence rates	Crude rates (95% CI)	Crude IRR (95% CI) Males vs females	Adjusted IRR* (95% CI) Males vs females
All psychoses			
Total	15.9 (13.7-18.1)		
Male	20.4 (16.8-24)	1.7 (1.3- 2.3)	1.7 (1.3-2.2)
Female	11.7 (9.1-14.3)		
Schizophrenia F20			
Total	9.6 (7.9-11.3)		
Male	13.1 (10.3-16)	2 (1.4-3)	2 (1.4-2.9)
Female	6.3 (4.4-8.2)		
Affective psychoses F30-33			
Total	1.5 (0.8-2.1)		
Male	1.8 (0.7-2.8)	1.5 (0.6-3.7)	1.4 (0.6-3.6)
Female	1.2 (0.4-2.0)		
Other psychoses F21-29			
Total	4.8 (3.6-6.0)		
Male	5.5 (3.7-7.4)	1.3 (0.8-2)	1.3 (0.8-2.1)
Female	4.2 (2.6-5.8)		

* IRR are adjusted by age and migration by Poisson Regression.

The crude incidence rate of all psychotic disorders was 15.9 per 100,000 person years (95% CI 13.7-18.1), 20.4 (95% CI 16.8-24) in males and 11.7 (95% CI 9.1-14.3) in females;

Crude incidence rate of schizophrenia was 9.6 per 100,000 per year (95% CI 7.9-11.3), 13.1 (95% CI 10.3-16) in males and 6.3 (95% CI 4.4-8.2) in females;

Crude incidence rate of affective psychoses was 1.5 per 100,000 per year (95% CI 0.4-1.5), 1.8 (95% CI 0.7-2.8) in males and 1.2 (95% CI 0.4-2) in females

Crude incidence rate of other non-affective psychoses was 4.8 (95% CI 3.6-6) per 100,000 per year, 5.5 (95% CI 3.7-7.4) in males and 4.2 (95% CI 2.6-5.8) in females.

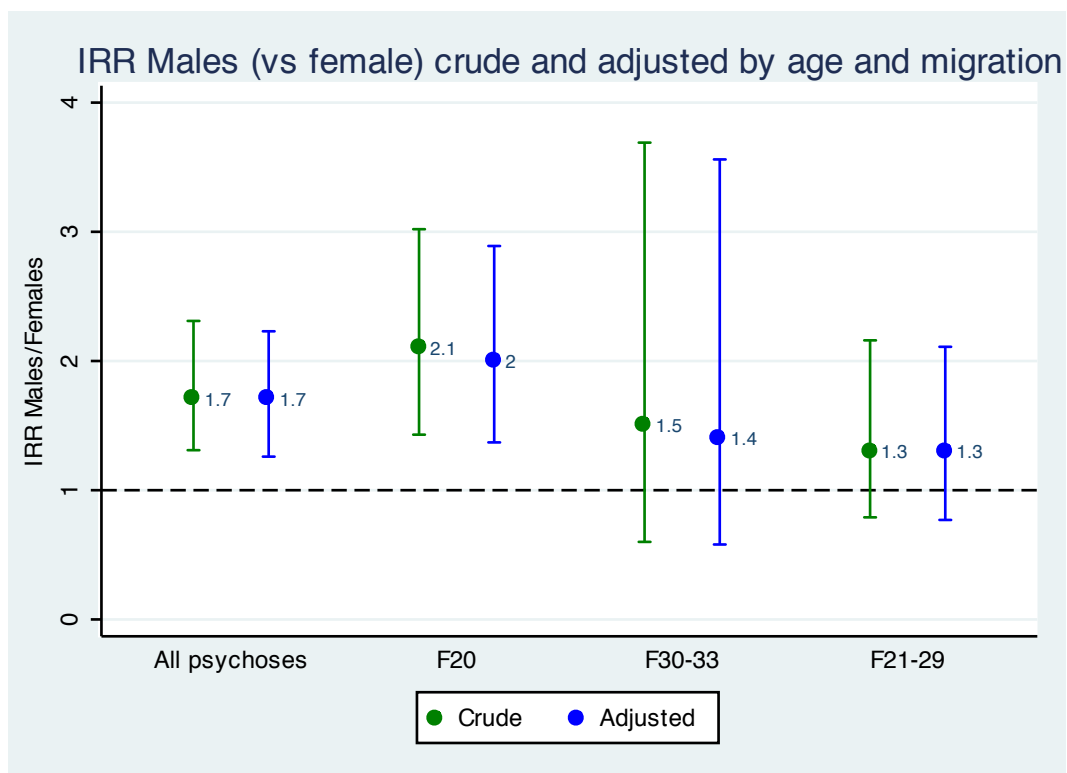
4.4.3 Is the risk of psychosis increased in males?

As shown in **Table 8**, incidence rates for overall psychoses and schizophrenia are higher in males. I applied Poisson regression model to evaluate if males had an increased risk than females to develop psychoses calculating the incidence rate ratio (IRR). I applied the likelihood ratio test (LRT) to test the interaction between age and migration and as shown by p values, I did not find any interaction between age and migration. I assume that IRR between males and females are homogeneous between native-born Italians and migrants for each age band.

Figure 13 shows crude and adjusted incidence rate ratios (IRR) for males and females by diagnostic category.

Males have a higher risk of developing any psychotic disorders (adjusted IRR: 1.7, 95% CI 1.3-2.2) than females; they also show a nearly double risk of developing schizophrenia when compared to females (adjusted IRR: 2, 95% CI 1.4-2.9). I did not find any difference by gender for affective psychoses and other non-affective psychoses.

Figure 13: crude and adjusted IRR (by age and migration) in males versus females for each diagnostic category



4.5 Incidence rates of psychosis in migrants

4.5.1 Introduction

Previous studies implicate migration as a risk factor for psychosis (Cantor Graae and Selten, 2005). In the AESOP studies certain minority ethnic groups were at higher risk for developing a psychotic disorder (Fearon, Morgan et al. 2006). There is now evidence that the incidence of all psychosis is higher in some migrant and minority ethnic populations in different countries (Europe, USA, Australia) (Morgan, Charalambides et al., 2010). In Italy Tarricone and colleagues found a higher risk for psychosis in migrants (IRR: 2.5, 95% CI 2.1-2.9) compared to native-born Italians (Tarricone, Mimmi et al. 2012).

I will describe differences in incidence rates in migrants and native-born Italians for overall psychosis and by diagnostic category; I will calculate the incidence rate ratios between native-born Italians and migrants to verify if migration is associated with an increased risk of developing psychotic disorders.

I will finally compare my results with the previous findings of the AESOP study.

4.5.2 Population denominator for migrants

Migrants who were resident in Palermo on 1^o January 2011 represented about 4% of the total resident population. The most numerous ethnic groups in Palermo come from Sri Lanka (17,3% of all migrants), followed by Bangladesh (17,0%) and Romania (11,0%) (ISTAT, www.tuttitalia.it/sicilia/81-palermo/statistiche/cittadini-stranieri-2011).

People aged 18-65 years belonging to ethnic minority group and resident in Palermo in 2011 were 15,142 (M: 7600, F: 7542).

4.5.3 Numerator for migrants

Over 204 cases, 183 (89.7%) were native-born Italians (white Italians) and 21 were migrants (10.3%): 7 females (33.3%), 14 males (66.7%).

Although migrants were only 21, their proportion exceeded that in the general population (10.3% versus 4%).

There were no differences in the proportion of males and females between native-born Italians and migrants. Male native-born Italians were 61.2% versus 66.7% of male migrants (chi=0.2, df=1, p-value 0.626, χ^2 test).

All migrants were people who were born in their country of origin (first generation migrants). The distribution of ethnicity among 21 migrants is showed in **Table 9**.

Table 9: ethnic groups among cases

	Total (%)	Males (%)	Females (%)
White Italians	183 (89.7%)	112 (88.9%)	71 (91%)
White Caucasian (Europe)	7 (3.4%)	2 (1.6%)	5 (6.4%)
Asians	7 (3.4%)	6 (4.8%)	1 (1.3%)
Africans	7 (3.4%)	6 (4.8%)	1 (1.3%)

1. 7 were white Caucasians from Eastern Europe (5 from Romania, 1 from Poland, 1 from Jugoslavia);
2. 7 came from Asia (4 Indian, 2 Bangladesh, 1 Philippines, 1 Afghanistan);
3. 7 came from Africa (2 Morocco, 2 Ghana, 1 Ivory Coast, 1 Tunisia (mixed Italian), 1 Mauritius).

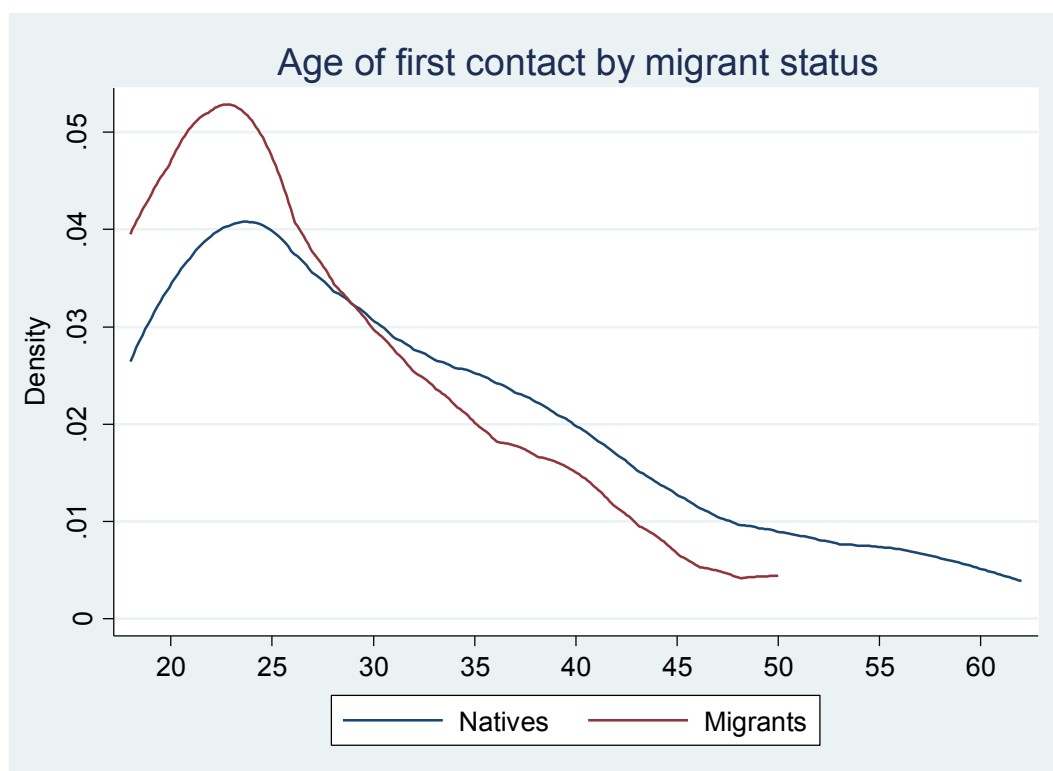
White Italians constituted the 89.7% of the sample. Migrants were equally distributed in the three wide categories (white Europeans, Asians and Africans). Africans and Asians were mostly males while Europeans migrants were mostly women.

17 migrants (80.95%) were diagnosed with schizophrenia, 4 (19.05%) were diagnosed with other psychosis. None received the diagnosis of affective psychosis (mania and depressive psychosis)

4.5.4 Age of first contact with mental health services in migrants

Median age at first presentation for all psychotic disorder was significantly different between native-born Italians (29, IQR 16) and migrants (25, IQR 10) ($z=2.0$, $p\text{-value}=0.049$, Wilcoxon test) as shown in **Fig 14** and **Table 10**.

Figure 14: age of first contact with mental health services in native-born Italians and migrants.



When we take into account all psychotic disorders, there is an earlier age at first presentation to psychiatric services for migrants ($z=2.0$, $p\text{-value}=0.049$, Wilcoxon test). However, when we look at the differences in the age at first presentation by each diagnostic category, the differences disappear. This is likely to be due to the small sample size of migrant group in this thesis.

In table **10** I report both mean and median age at first contact with psychiatric services but I compared median age between native-born Italians and migrants applying Wilcoxon test because of an asymmetric distribution of age.

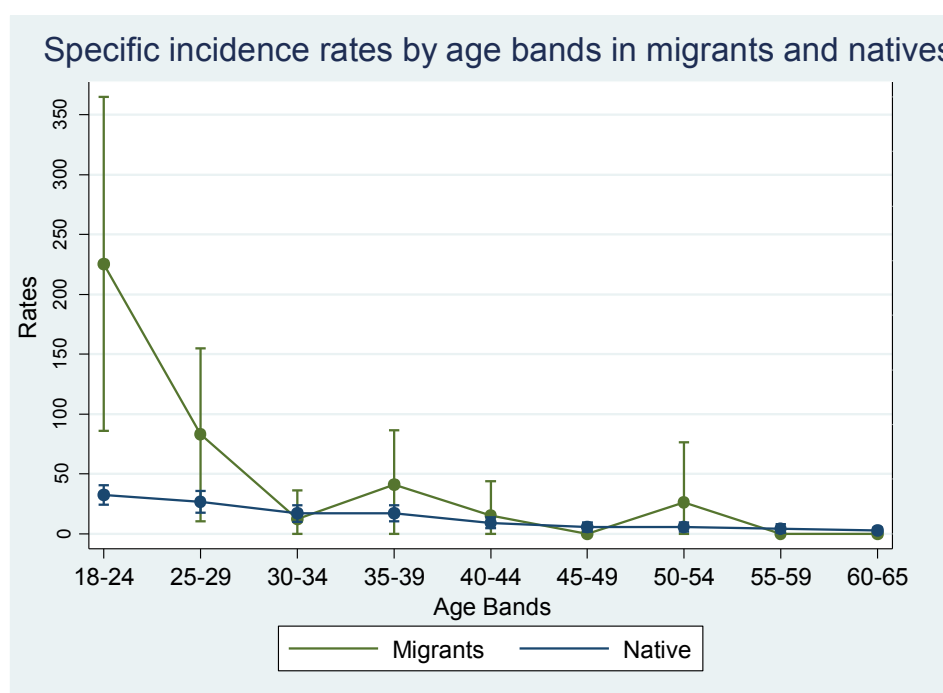
Table 10: mean and median age at first presentation by each diagnostic category by migrant status. p value refer to median age at first contact.

Diagnosis	Mean age of first contact (sd)	Median age of first contact (IQR)	P value*
All psychoses F20-33			
Native-born Italians	31.7 (11.3)	29 (16)	0.049
Migrants	26.7 (8.7)	25 (10)	
Schizophrenia F20			
Native-born Italians	30.2 (11.2)	26 (15)	0.130
Migrants	25.8 (8.4)	24 (8)	
Affective Psychosis F30-33			
Native-born Italians	29.8 (10.3)	29(13)	-
Migrants	-	-	
Other psychosis F21-29			
Native-born Italians	35.2 (11.3)	33 (8)	0.473
Migrants	31 (10.1)	33 (10)	

*p value from Wilcoxon test

Fig 15 shows specific incidence rates by age bands for migrant and native-born Italians.

Figure 15: specific incidence rates and their 95% CI by age bands in migrants and native-born Italians.



When we look at specific rates there is a statistically significant difference in the incidence of psychosis in native-born Italians and migrants for the age band 18-24 while from 30-34 years the curves tend to overlap **Fig 15**. As shown in **Table 11**, most of the migrants (47.6%) belong to the age band 18-24. It is possible that young people are more likely to have migrated recently and therefore the stress of migration might cause them to develop psychosis.

Table 11: distribution of migrants and native-born Italians by age bands

	Migrants, n (%)	Native-born Italians, n (%)
18-24	10 (47.6)	61 (33)
25-29	5 (23.9)	34 (18.6)
30-34	1 (4.7)	22 (12)
35-39	3 (14.3)	25 (13.7)
40-44	1 (4.7)	14 (7.6)
45-49	0	9 (4.9)
50-54	1 (4.7)	8 (4.3)
55-59	0	6 (3.3)
60-65	0	4 (2.2)
Total	21	183

4.5.5 Is the risk of psychosis increased in migrants?

Table 12 shows crude incidence rates and their 95% CI for native-born Italians and for migrants for all psychoses and by diagnostic category. Crude and adjusted incidence rate ratios (IRR) and their 95% CI are presented for each diagnostic category.

I applied Poisson regression to calculate the incidence rate ratio between migrant and native-born Italians after adjusting for age and sex. Likelihood ratio test (LTR) excluded interaction between age and gender as shown in **Table 12**.

The incidence rates for all psychoses were 14.8 (95% CI 12.6-16.9) in native-born Italians and 46.2 (95% CI 26.5-66) in migrants.

For schizophrenia, incidence rates were 8.6 (95% CI 6.9-10.2) in native-born Italians and 37.4 (95% CI 19.6-55.2) in migrants and for other non-affective psychoses incidence rates were 4.7 (95% CI 3.5-5.9) in native-born Italians and 8.8 (95% CI 0.2-17.4) in migrants.

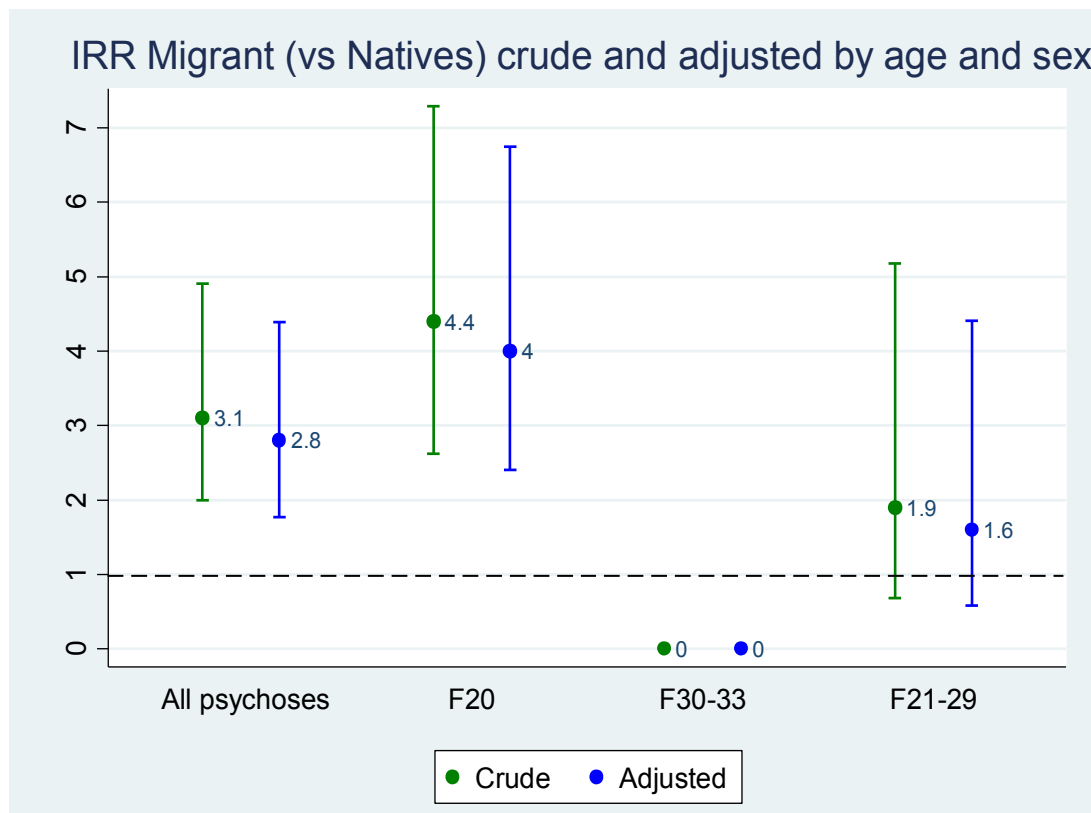
Affective psychosis was only present among native-born Italians with an incidence rate of 1.5 (95% CI 0.8-2.1).

Table 12: Crude incidence rates in native-born Italians and migrants for all psychosis and by diagnostic category (rates are displayed per 100,000 persons per year). Crude and adjusted (by age and gender) incidence rate ratio (IRR) with their 95% for migrants and native-born Italians.

Incidence rates	Crude rates (95% CI)	Crude IRR (95% CI)		Adjusted IRR (95% CI)*	
		Migrants native-born Italians	vs	Migrants native-born Italians	vs
All psychosis					
Native-born Italians	14.8 (12.6-16.9)	3.1 (2-5)		2.8 (1.8-4.4)	
Migrants	46.2 (26.5-66)				
Schizophrenia F20					
Native-born Italians	8.6 (6.9-10.2)	4.4 (2.6-7.3)		4 (2.4-6.7)	
Migrants	37.4 (19.6-55.2)				
Affective psychoses F30-33					
Native-born Italians	1.5 (0.8-2.1)	-		0	
Migrants	0				
Other psychoses F21-29					
Native-born Italians	4.7 (3.5-5.9)	1.9 (0.7-5.2)		1.6 (0.6-4.4)	
Migrants	8.8 (0.2-17.4)				

*IRR are adjusted by age and gender by Poisson Regression.

Figure 16: crude and adjusted (by age and gender) incidence rate ratio in migrants versus native-born Italians.



Migrants have a nearly 3 fold increased risk to develop any psychotic disorder (adjusted IRR: 2.8, 95% CI 1.8-4.4) and they have 4 fold increased risk of developing schizophrenia (adjusted IRR: 4, 95% CI 2.4-6.7) compared to native-born Italians. No difference in risk has been found for other psychotic disorders (**Fig. 16**).

These results are in line with the existing literature. In the AESOP study the differences in incidence rates are described in details for groups of ethnic minorities rather than for native British and migrant people; Afro-Caribbeans for example showed an IRR of 6.7 (95% CI 5.4–8.3) to develop psychotic disorders compared to white British (Fearon, Kirkbride et al. 2006).

4.6 Comparing incidence rates of psychosis in Palermo to AESOP

After calculating crude and adjusted incidence rates and incidence rate ratios (IRR) for gender and migration in Palermo sample, I was interested

in comparing my data to that of AESOP to see whether there was a variation in the incidence of overall psychoses and in different diagnostic categories.

4.6.1 Differences between Palermo and AESOP cases

The Palermo sample included 204 cases, the AESOP sample 360 (after manipulating the dataset to exclude second generation migrants, cases aged less than 18 years and Bristol cases).

In Palermo sample 60% of cases were affected by schizophrenia, 9.3% by affective psychoses, 30.4% non-affective psychoses. In the AESOP sample 45% were schizophrenic, 26% were diagnosed with affective psychosis, 29% with other non-affective psychoses.

For overall psychoses, there were no significant differences between the distribution of AESOP and Palermo cases by age-bands (Pearson $\chi^2=8$, $df=8$, $p=0.433$) and by gender (Pearson $\chi^2=0.17$, $df=1$, $p=0.680$).

In the original AESOP sample, median age at first presentation was 27 years (IQR:12) in males and females 30 years in females (IQR 15) (Kirkbride, Fearon et al. 2006). In Palermo median age at first contact was similar to that found in the AESOP study: median age at first presentation in Palermo was 26.5 (IQR:13) in males and 32.5 (IQR:16) in females.

There was a different proportion of migrants in the Palermo and AESOP samples (Pearson $\chi^2 =52.2$, $df=1$, $p<0.001$). In AESOP 61.1% of the sample were UK-born people versus 38.9% Non-UK born. In Palermo non-Italy born people were just the 10.3% of the sample.

There was a different distribution of schizophrenia by age-bands between Palermo and AESOP (Fisher test, $p=0.03$). The proportion of schizophrenic patients was higher in Palermo (40.6%) than AESOP (28.4%) in the age band 18-24, while it was higher in AESOP (18.5%) compared to Palermo (8.9%) in the age band 30-34. The proportion of migrants among schizophrenic patients was significantly higher in the

AESOP sample (47%) compared to Palermo (13.8%) (Pearson $\chi^2=34.3$, $df=1$, $p<0.001$).

No differences have been found in the distribution of affective psychoses by age-band (Fisher test, $p=0.945$) and gender (Pearson $\chi^2=0.45$, $df=1$, $p=0.505$) between Palermo and AESOP samples. There were not any migrants affected by affective psychosis in Palermo sample. In the AESOP sample the distribution of affective psychoses was 39.2% in migrants and 60.8% in UK born people.

No differences have been found in the distribution of other non-affective psychoses by age-bands (Fisher test, $p=0.863$) and gender (Pearson $\chi^2=0.06$, $df=1$, $p=0.796$) between Palermo and AESOP samples. There was a higher proportion of migrants affected by other psychoses in the AESOP sample (34.8%) compared to Palermo (6.4%).

4.6.2 Incidence rates differences between Palermo and UK

To take into account the difference distribution of age and gender in the population structure of Palermo and UK, I standardized incidence rates by age and gender.

I used indirect standardization, applying age and sex specific rates of AESOP sample to Palermo population (see the chapter of methods for further details).

Fig 17 shows Palermo age and sex standardized incidence rates for all psychoses and for each diagnostic category, compared to AESOP rates. AESOP rates differ from those reported by Kirkbride and colleagues in their paper (Kirkbride, Fearon et al., 2006) because AESOP incidence rates have been recalculated just for London and Nottingham and excluding Bristol because of the lack of data on place of birth which I used to adjust for migration status (see methods for further details).

As explained in detail in the previous chapter, AESOP specific incidence rates have been recalculated excluding second-generation migrants (people who were born in UK but from migrant parents). In this work I

compared native-born Italians in Palermo with white British in AESOP, and migrants in Palermo to non-UK born people in AESOP.

Figure 17: standardized incidence rates in Palermo by age and gender.

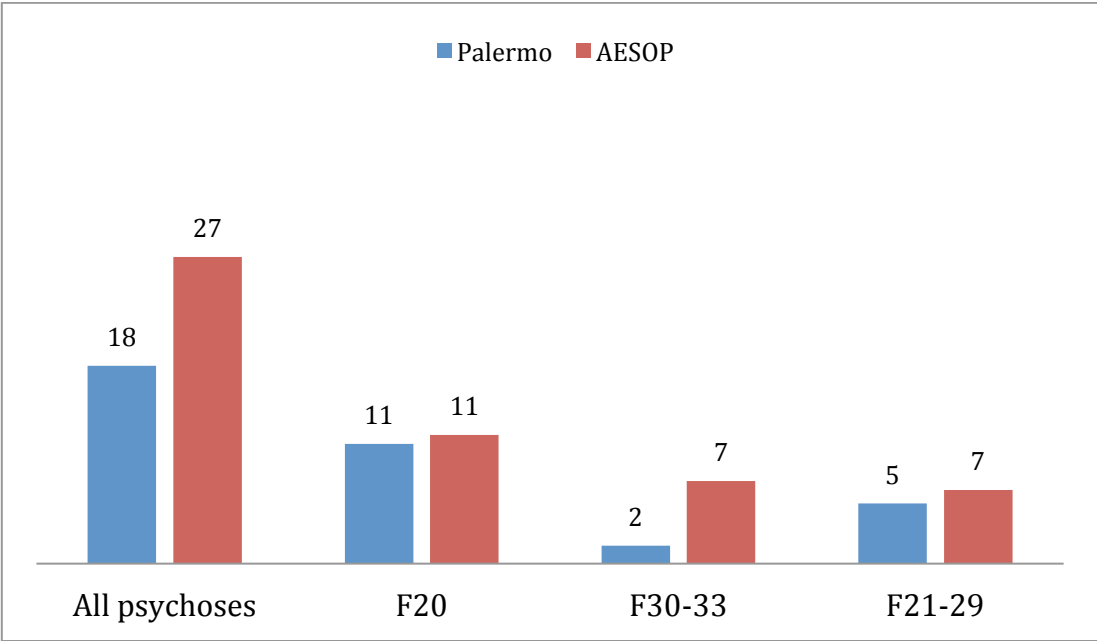


Table 13 shows the standardized rates by age and sex for Palermo compared to the standardized rates in AESOP.

In the table I also reported the standardized morbidity ratio (SMR) and its reciprocal (1/SMR) with its 95% CI to compare incidence rates in Palermo and AESOP.

The SMR measures how much more or less likely a person is to develop a disorder in the study population compared to someone of the same age and sex in the standard population (AESOP). If the value is close to 1, there are no differences in the likelihood of developing the disorder, a value smaller than 1 means that subjects are less likely to become ill compared to the standard population (Kirkwood and Sterne, 2006).

Fig 18 graphically shows all the 1/SMR for all psychoses and by each diagnostic category displaying the increased risk in UK compared to Palermo.

After standardizing for age and sex, people in Palermo are less likely to develop any psychotic disorder than in London and Nottingham.

In AESOP the risk of developing any psychotic disorder is 1.5 higher than in Palermo with a SMR: 0.6 (95% CI 0.6-0.7).

I did not find any difference in the risk of developing schizophrenia in UK and in Palermo respectively SMR: 0.9 (95% CI 0.7-1.1).

No statistical differences were found between the incidence of non-affective psychoses in the two sites.

The most relevant difference is the increased risk of developing an affective psychotic disorder in London and Nottingham when compared to Palermo. In UK the risk of affective psychoses is 4.5 higher than in Palermo with a SMR of 0.2 (95% CI 0.1-0.3).

So the excess of psychosis in UK appears to be due to the higher incidence of affective psychoses in UK when compared to Palermo.

Table 13: comparison of standardized (by age and sex) incidence rates by diagnostic categories in Palermo and in AESOP.

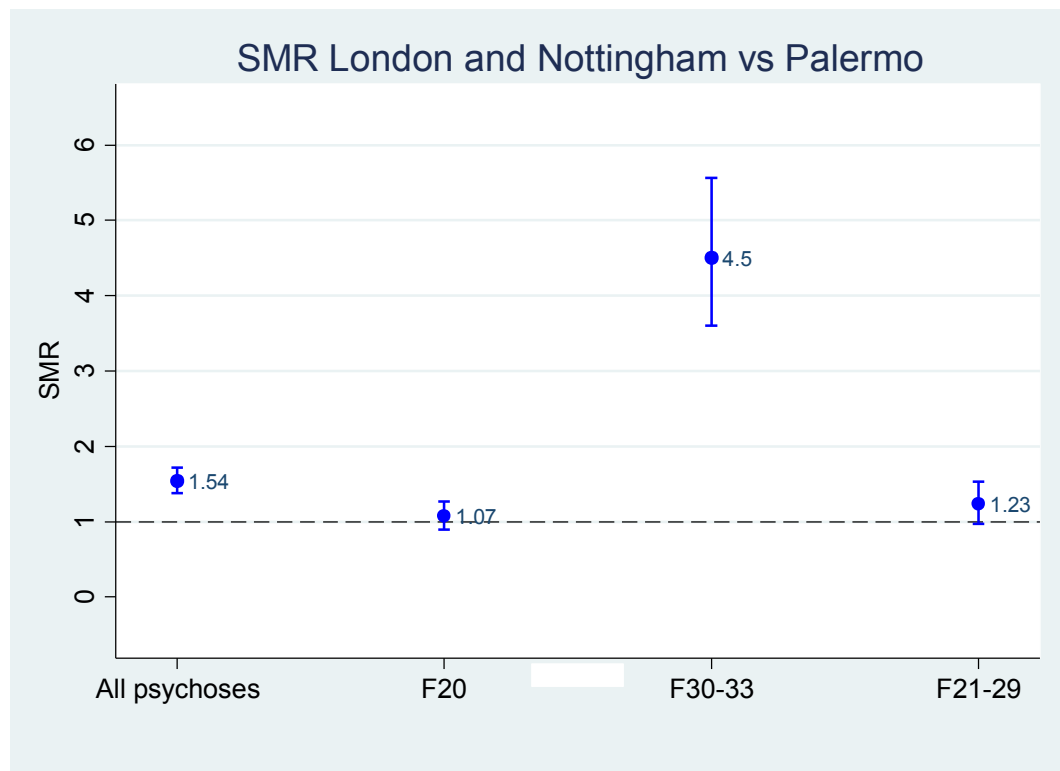
Incidence rates	Standardized rate Palermo by age and sex (95% CI)	Rates AESOP (London and Nottingham) (95% CI)	SMR (95% CI) 1/SMR (95% CI)
All psychoses	17.5 (15.2-20.1)	27.1 (24.4-30)	0.6 (0.6-0.7) 1.5 (1.3-1.7)
F20	10.6 (8.8-12.7)	11.4 (9.6-13.3)	0.9 (0.7-1.1) 1.07 (0.9-1.3)
F30-33	1.6 (1-2.5)	7.3 (5.9-8.9)	0.22 (0.1-0.3) 4.5 (3.6-5.6)
F21-29	5.3 (4-6.7)	6.5 (5.2-8)	0.8 (0.6-1) 1.2 (1-1.5)

I then stratified the SMR by migration status (**Table 14**). As reported by the SMR values, British natives show a higher risk of developing psychoses than Palermo natives-Italian. There were no differences in the risk of overall psychosis or its subcategories among non-natives in the two countries. There appears to be an increased risk of affective psychoses in British natives compared to Italian natives SMR: 0.3 (0.2-0.4).

Table 14: Comparison of standardized (by age and sex) incidence rates in Palermo and in AESOP stratified by migration status; SMR refer to the different risk in native born Italians and British natives and in Palermo migrants vs non-British AESOP cases.

Incidence rates	Palermo incidence rates by age and sex (95% CI)	AESOP incidence rates (London and Nottingham) (95% CI)	SMR (95% CI)
All psychoses			
Natives	16.5 (14.2-19.1)	20.6 (18-23.5)	0.8 (0.7-0.9)
Migrants	46.2 (28.2-70)	53.3 (44.8-62.9)	0.8 (0.5-1.3)
F20			
Natives	9.9 (8.1-12)	7.5 (5.9-9.3)	1.3 (1-1.6)
Migrants	37 (21.5-59.2)	27 (21.1-34)	1.4 (0.8-2.2)
F30-33			
Natives	1.6 (1-2.5)	5.5 (4.2-7.1)	0.3 (0.2-0.4)
Migrants	0	0	
F21-29			
Natives	5.1 (3.9-6.6)	5.2 (3.9-6.8)	0.9 (0.7-1.3)
Migrants	8.6 (2.2-22.1)	11.4 (7.7-16.3)	0.7 (0.2-1.9)

Figure 18: reciprocal of SMR ($1/\text{SMR}$) and 95% CI for all psychoses and by each diagnostic category (after standardizing by age and gender).



4.7 Comparing incidence rates of psychosis in Palermo to AESOP after standardizing for migration

Since in AESOP the proportion of people belonging to ethnic minorities in the sample was higher (38.9%) compared to Palermo (10.3%), I further standardized for migration (together with age and gender) in order to take into account the differences of the structure of the two samples (age, gender, migration). However, in AESOP there is a detailed description of ethnic minorities but there is not a specific category of “migrant”. To compare Palermo and AESOP data I defined non-UK born people as migrants, as described in chapter 3.

Fig 19 shows Palermo standardized incidence rates (by age, sex and migration) for all psychoses and for each diagnostic category, compared to AESOP rates.

Table 15 and **Fig. 20** show Palermo standardized incidence rates for overall psychoses and for each diagnostic category; the SMR and its reciprocal 1/SMR displays the reciprocal of the SMR for each category.

Fig 19: standardised incidence rates in Palermo and AESOP (by age, gender and migration).

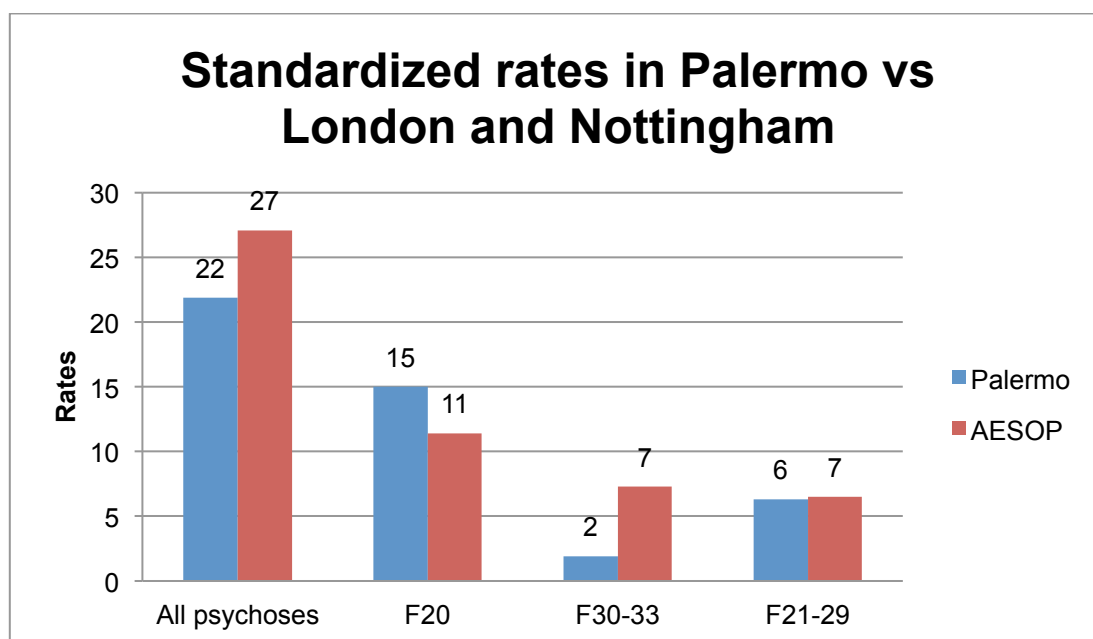
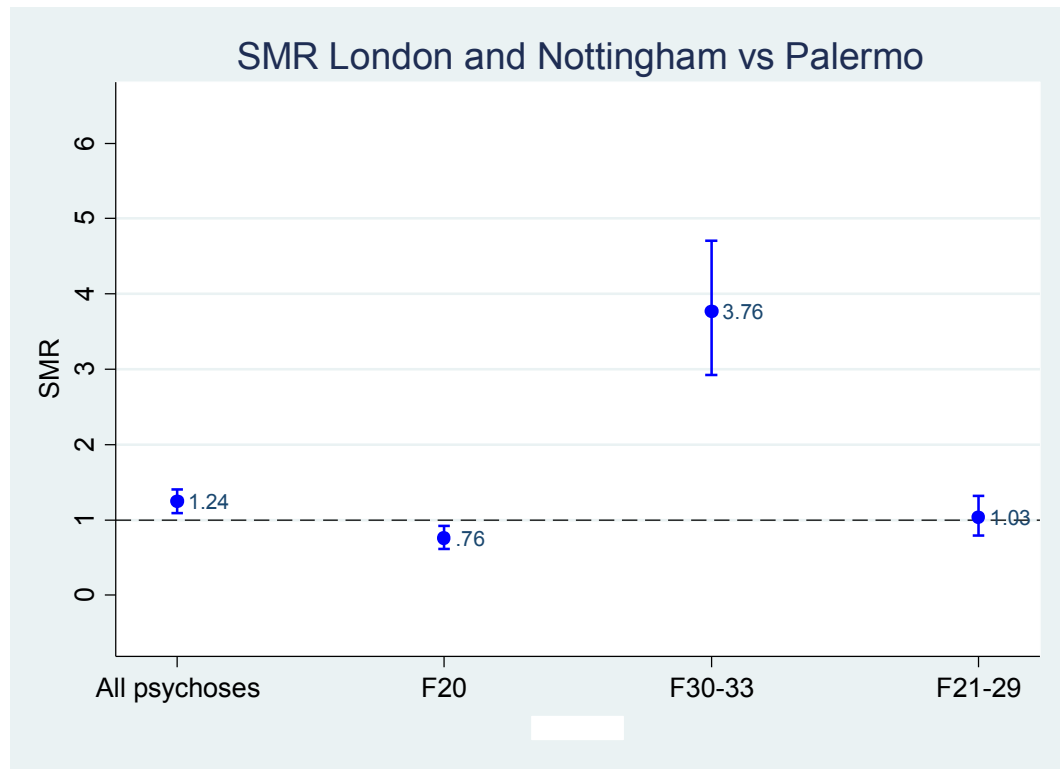


Table 15: comparison of standardized incidence rates (by age, sex and migration) by diagnostic categories in Palermo and in AESOP.

Incidence rates	Standardized rate Palermo by age, sex and migration	Rates AESOP (London and Nottingham)	SMR (95% CI) 1/SMR (95% CI)
All psychoses	21.9 (19-25.1)	27.1 (24.4-30)	0.8 (0.7-0.9) 1.2 (1.1-1.4)
F20	15 (12.5-17.9)	11.4 (9.6-13.3)	1.3 (1.1-1.6) 0.7 (0.6-0.9)
F30-33	1.9 (1.2-3)	7.3 (5.9-8.9)	0.3 (0.2-0.4) 3.8 (2.9-4.7)
F21-29	6.3	6.5 (5.2-8)	0.9 (0.7-1.2) 1.04 (0.8-1.3)

Figure 20: reciprocal of SMR (1/SMR) and 95% CI for all psychoses and by each diagnostic category (after standardizing by age, gender and migration).



After standardizing for age, gender and migration rates in Palermo the magnitude of the difference in risk of psychoses between AESOP and Palermo was slightly reduced and the risk of all psychoses was 1.2 higher in AESOP when compared to Palermo; 1/SMR: 1.2 (95% CI 1.1-1.4)

There was still an increased risk for developing affective psychoses in UK: SMR: 0.26 (95% CI 0.2-0.4) but schizophrenia rates were higher in Palermo than in UK: SMR=1.3 (95% CI 1.08-1.6).

There was not any difference in the risk of other non-affective psychoses between the two sites: SMR: 0.9 (95% CI 0.7-1.2).

So, assuming that Palermo and AESOP had the same structure in terms of age, gender and migration the risk was still modestly increased for overall psychoses in UK and substantially increased for affective psychoses in UK compared to Palermo.

These results off the possibility of some speculations about the underlying reasons for these differences which will be discussed in chapter 6.

4.8 Summarizing the results

1. I identified 204 cases of first episode of psychosis over 3 years in Palermo 61.8% were males.
2. The median age at first presentation for all psychoses was 28 years (IQR 16); Males had an earlier onset 26.5 (IQR:13) than females 32.5 (IQR:16), ($z=2.3$, $p\text{-value}=0.020$, Wilcoxon test),. Migrants had an earlier median age at first presentation (25 years, IQR 10) than native-born Italians (29, IQR 16) ($z=2.0$, $p\text{-value}=0.049$, Wilcoxon test).
3. The incidence rate for all psychotic disorders was higher in males: IRR: 1.7 (95% CI 1.3-2.2).
4. Migrants were more likely to develop any psychosis: IRR: 2.8 (95% CI 1.7-4.4).
5. Incidence rates of overall psychoses were lower in Palermo than AESOP after standardizing for age and sex; no differences were found in the risk of developing schizophrenia and other non-affective psychoses. So the difference in the overall rate might be explained by the lower rates of affective psychoses.
6. After introducing as explanatory variable migration to age and sex, the overall rates of psychoses remained slightly increased in UK than in Palermo. Schizophrenia risk tend to be higher in Palermo while affective psychoses risk was increased in UK

Chapter 5

Risk factors associated with Psychosis

5.1 Introduction

Several social and biological risk factors have been associated with an increased risk of psychotic disorder (e.g family history for psychiatric disorders and for psychosis in first-degree relatives, cannabis and other drug consumption, childhood and adult adversities and experiences of victimization) (Stilo, Murray, et al., 2010).

5.2 Case control aims

I carried out a case control analysis in a subsample of the FEP patients identified for the incidence study, aimed at:

1. Comparing the prevalence of certain supposed environmental risk factors for psychosis in patients affected by a first episode of psychosis, and in healthy controls.
2. Comparing the prevalence of environmental risk factors between Palermo sample of cases and controls and similar samples of first episode psychotic patients recruited in London (Genetic and Psychosis Study and AESOP study).

5.3 Hypothesis

According to the literature, I expect a different prevalence of the main risk factors between cases and controls (history of psychiatric disorder in the family, cannabis and other illicit drug exposure, adverse childhood experiences and victimization experiences lifetime).

I expect similarities in the prevalence of some of the risk factors as reported in the GAP and AESOP studies e.g. family history for psychiatric disorders, adverse childhood experiences and lifetime victimization experiences but I expect differences in the prevalence of cannabis exposure in cases and controls between Italy and UK because of the

differences in the prevalence of lifetime cannabis consumption in the general population in the two sites (22.4% in Italy, 40% in UK).

5.4 Methods and assessment

During the study period, we recruited 68 subjects affected by psychosis at their onset out of 204 patients identified for the incidence study. They accepted to be enrolled in the Sicilian Genetics and Psychosis study. All the patients fulfilled the criteria for an ICD 10 diagnosis of psychosis. The diagnoses were confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992). Socio-demographic data were collected by The Modified version of the Medical Research Council (MRC) socio-demographic scale (Mallett, Leff et al. 2002).

Over the same period, we recruited a sample of 74 healthy controls from the local population. They were similar to cases in terms of gender, migration status, while there were differences for age, level of education and employment status. All the comparisons were then adjusted for these differences.

Table 16 shows the instruments used for the assessment of the risk factors in cases and controls.

Table 16: instruments for the assessment of genetic and environmental risk factors

Risk factor	Questionnaire/Scale
Family History of Psychiatric disorder	Family Interview for Genetic study (FIGS) (NIMH Genetic Initiative)
Cannabis and Other drug consumption	Cannabis Experience Questionnaire modified version (Di Forti, et al 2009)
Childhood traumatic experiences	Childhood Experience of Care and Abuse (CECA) Questionnaire modified version (Bifulco et al., 2005),
Adult adverse life events	Brief Life Events schedule modified version (adapted from Bebbington et al. 2004)
Cognitive assessment	Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981)

Patients were further assessed by:

- Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein 1987): was used to evaluate symptom severity.
- Nottingham onset schedule (NOS DUP) (Singh 2005): is a short interview and rating schedule to measure onset in psychosis.
- Wechsler Adult Intelligence scale (WAIS-R) (Wechsler, 1981): was used to measure IQ in cases and controls.

5.5 Statistics

Logistic regression was used to analyze the association between the main risk factors studied and the presence of a psychotic disorder, after adjusting for potential confounders.

5.6 Results

5.6.1 Description of the sample

68 first episode patients (FEP) (33.3%) out of 204 patients were recruited into the study and completed the whole assessment.

136 (66.6%) patients were not involved in the study either because they refused to be interviewed (72, 53%) or because they had been screened and identified retrospectively (64, 47%) or by the leakage study (see methods for further details).

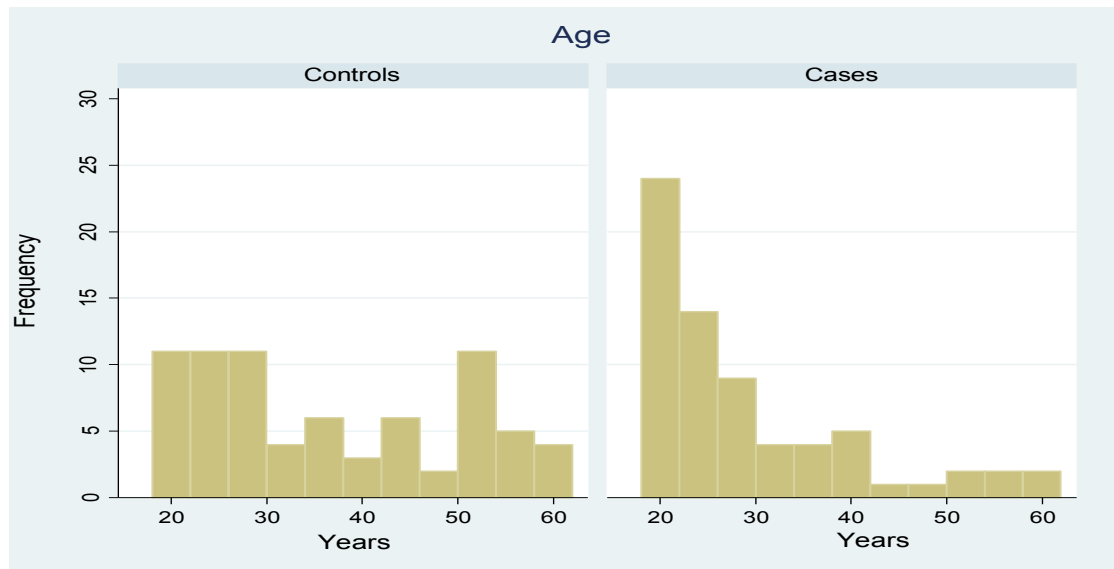
We also recruited 74 healthy controls aged 18 to 65 years from the local population (see chapter 3 for details about control recruitment). Case and controls characteristics are displayed in **Table 17**.

There was no difference of gender distribution between the two groups ($\chi^2=2.1$, $df=1$, p -value 0.147, χ^2 test).

Age at first contact with psychiatric services was used as an estimate of the age of onset of psychosis. This represents just a rough measure of the true onset of the disorder, since psychotic disorder often develop in a subtle way and sub-threshold symptoms are often present several years before the full expression of the disorder. Previous studies considered the

date of first contact with services as a proxy for date of onset of psychotic disorders (Sartorius, Jablensky et al. 1989; Eranti, Maccabe et al. 2013). There was a significant difference in terms of median age of cases (24 years; IQR 13) than controls (33.5 years; IQR 28) ($z=3.5$, $p\text{-value}<0.001$, Wilcoxon test) (**Fig. 21**) so all the analyses have been adjusted by age.

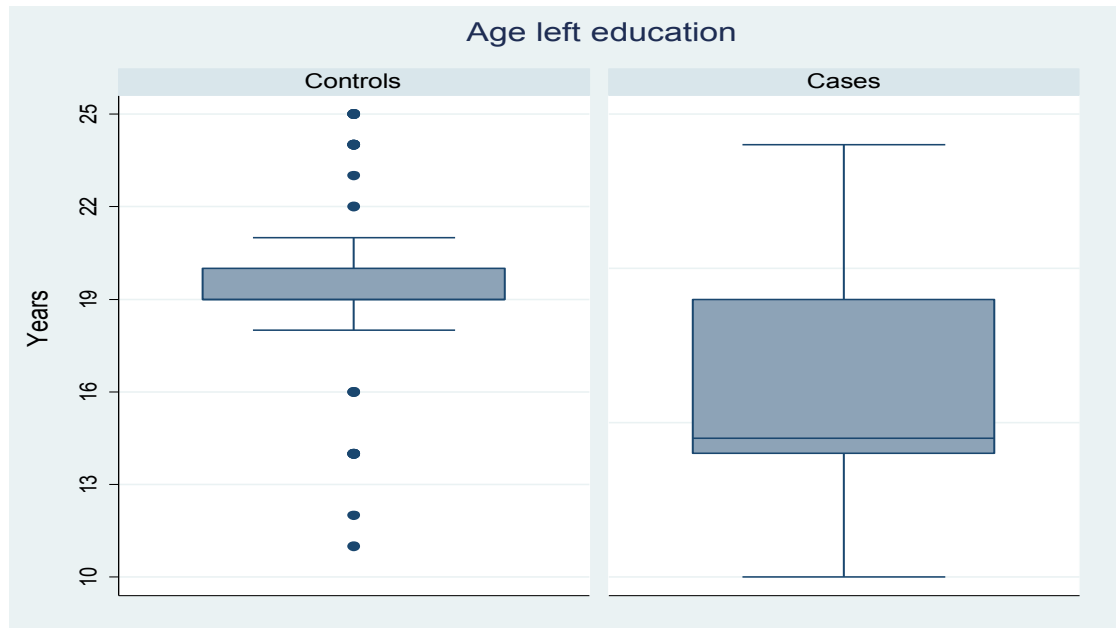
Figure 21: age distribution in cases and controls.



Cases had a significantly lower mean IQ (mean 78.7, sd:16.8) than controls IQ (mean 101.6, sd:23) ($t=5.8$, $df=86$, $p<0.001$, Welch test), however only half of the cases completed the assessment so the result must be interpreted cautiously. Most of the cases and controls were native-born Italians.

Cases were more likely to be less educated than controls ($\chi^2=21.6$, $df=1$, $p\text{-value}<0.001$, χ^2 test) and were also more likely to have reached primary school and junior high certificate ($p\text{-value}<0.001$, Fisher test).

Figure 22: mean age of leaving education in cases and controls.



Mean age of leaving education was 3 years earlier for cases than controls (**Fig. 22**) ($t=5.5$, $df=115$, $p<0.001$, Welch test).

Cases were also more likely to be unemployed compared to controls ($\chi^2=29.7$, $df=3$, $p<0.001$, χ^2 test). Cases were 6.7 times more likely to be single, separated or divorced than controls ($\chi^2=26.6$, $df=1$, $p<0.001$, χ^2 test), OR:6.7 (95%CI: 3.15-14.3). Controls were more likely than patients to have been ever involved in a long-term relationship ($\chi^2=10.5$, $df=1$, $p<0.001$, χ^2 test).

Table 17: sample characteristics of cases and controls

	Cases (68)	Controls (74)	P value*
Age, years mean (s.d.)	28.25 (11.2)	36 (13.2)	
Median (IQR)	24 (13)	33.5 (28)	<0.001
No details	-	-	
Gender, n (%)			
Male	44 (64.7)	39 (52.7)	0.147
Female	24 (35.3)	35 (47.3)	
No details	-	-	
IQ (WAIS) mean (sd)	78.71 (16.81)	101.58 (23.05)	<0.001
No details	34	-	
Migration status, n (%)			
Natives	60 (88.2)	70 (94.6)	0.174
Migrant	8 (11.8)	4 (5.4)	
No details	-	-	
Ethnicity, n (%)			0.710
Caucasian	64 (94.1)	71 (95.95)	
non Caucasian	4 (5.9)	3 (4.05)	
No details	-	-	
Level of education, n (%)			
No education	0	2 (2.7)	<0.001
Primary school	9 (13.4)	1 (1.4)	
Junior High	26 (38.8)	13 (17.8)	
Diploma	30 (44.8)	47 (64.4)	
University	2 (3)	10 (13.7)	
No details	1	1	
Mean age left education, sd	16 (2.91)	19.3 (3.5)	<0.001
No details	1	1	
Employment, n (%)			
Unemployed	41 (61.2)	17 (23)	<0.001
Employed	14 (20.9)	35 (47.3)	
Student	12 (17.9)	11 (14.9)	
Retired	0	11 (14.9)	
No details	1	-	
Relationship status, n (%)			
In a stable relationship	14 (20.6)	47 (63.5)	<0.001
Single/separated/divorced	54 (79.4)	27 (36.5)	
No details	-	-	

* p value from t tests, Wilcoxon test, χ^2 tests, Fisher's tests

Table 18 summarizes the main characteristics of cases. 72% of cases had a diagnosis of schizophrenia.

Median age at first presentation of psychosis did not differ significantly in males and females ($z=0.9$, $p\text{-value}=0.382$, Wilcoxon test).

Mean score for PANSS cases was 102.27 (sd:25.1). I did not find any difference in mean PANSS score by gender ($t=-0.3$, $df=57$, $p\text{-value}=0.784$, Student t-test).

Mean duration of untreated psychosis (DUP) was 5.8 months, sd 9.4. Applying Wilcoxon test did not show any difference in DUP by gender ($z=-1.6$, $p\text{-value} 0.094$, Wilcoxon test).

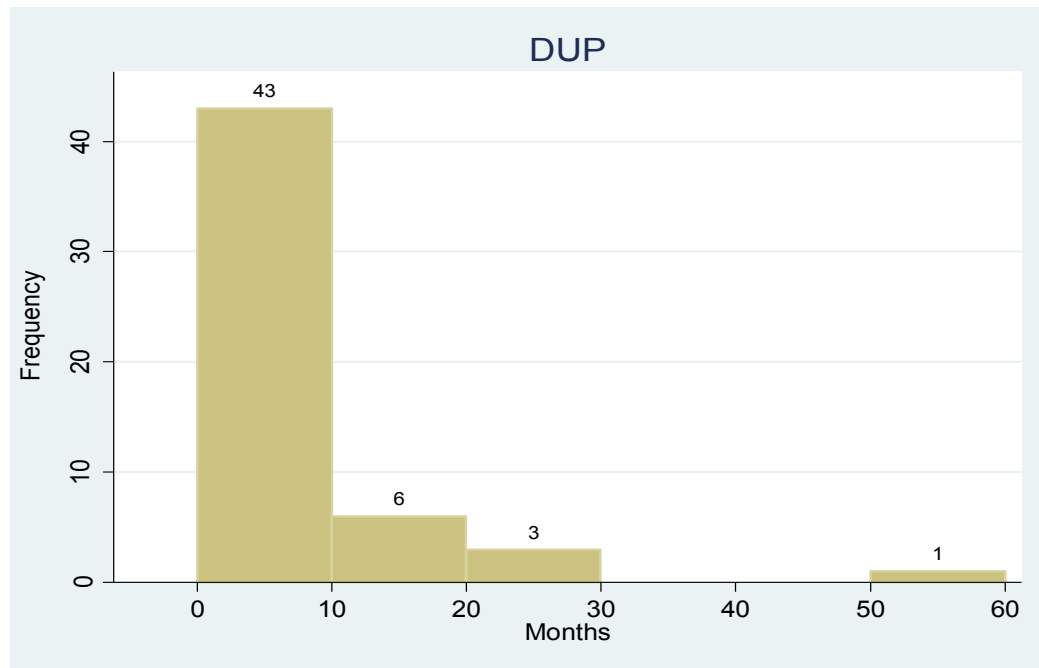
Table 18: clinical characteristics of cases

Cases	68	p value*
Diagnosis, n (%)		
Schizophrenia	49 (72)	
Manic psychosis	2 (2.9)	
Depressive psychosis	3 (4.4)	
Other psychosis	14 (20.6)	
Median age at first presentation, years (IQR)		
Males	23.5 (11.5)	0.382
Females	26.0 (17.5)	
PANSS mean score, (sd)		0.784
Total	102.3 (25.1)	
Males	102.9 (26.7)	
Females	101 (22.5)	
No details	9	
Mean duration of untreated Psychosis (DUP) in months, (sd)		
Total	5.8 (9.4)	
Males	5.7 (13.4)	0.094
Females	5.9 (6.4)	
No details	15	

* p value from t test, Wilcoxon test

As shown in **Fig. 23** most of the cases (43, 63.2%) have a duration of untreated psychosis between 0 and 10 months.

Figure 23: duration of untreated psychosis (DUP) in cases.



5.6.2 Psychiatric family history

According to the literature, schizophrenia has a strong familial component (Kendler, McGuire, et al. 1993). Patients affected by schizophrenia are more likely to have one or more first-degree relatives affected by any psychiatric disorder than healthy individuals (Byrne, Agerbo et al. 2002). Patients with a higher familial load of psychosis have an earlier age of onset of the disorder (Suvisaari, Haukka et al. 1998).

5.6.2.1 Aims

- Comparing the prevalence of any psychiatric disorders and psychotic disorders in the first-degree relatives of cases and controls.
- Comparing the mean age at first presentation among cases in those with and without family history for psychosis.

5.6.2.2 Hypothesis

1. I expect cases to have a higher prevalence of a history of any psychiatric disorder and of psychotic disorders in first generation degree relatives.
2. I expect cases with a first-degree relative affected by a psychotic disorder to have an earlier age at first presentation than those without.

5.6.2.3 Methods

I have used χ^2 to test for association between any psychiatric disorder in the family and the risk of being a patient.

Due to the small number of controls (2) with a first-degree relative affected by psychosis, I used Fisher exact test to test for the association of having a first-degree relative affected by a psychotic disorder and the probability of being a case.

I applied logistic regression to calculate adjusted OR for potential confounders (age, gender, education, employment). I selected the confounders according to the main socio-demographic differences in the two groups (χ^2 , Welch test).

I used Welch test to evaluate the association between mean age at first presentation in cases and any psychiatric disorder in the family.

5.6.2.4 Results

Table 19 shows the proportion of any psychiatric disorder and of psychotic disorders among first-degree relatives in patients and controls.

Cases were more likely than controls to have a first-degree relative affected by any psychiatric disorder ($\chi^2=14.2$, $df=1$, $p\text{-value}<0.001$, χ^2 test), and they were more likely to have a first-degree relative affected by a psychotic disorder ($\chi^2=15.1$, $df=1$, $p\text{-value}<0.001$, χ^2 test).

Among cases, those with a family history of psychiatric disorder had an earlier mean age at first presentation (24.9 yrs, sd 7.8) than those without (31, sd 13) ($t=2.3$, $df=56$, $p\text{-value}=0.025$, Welch test).

Table 19: psychiatric family history in cases and controls

	Cases (68)	Controls (74)	OR
Any psychiatric disorder in first-degree relatives, n (%)			
Yes	28 (44.4)	11 (15)	<0.001
No	35 (55.6)	62 (85)	
No details	5	1	
Psychosis in first-degree relatives, n (%)			<0.001
Yes	16 (25.4)	2 (2.7)	
No	47 (74.6)	71 (97.3)	
No details	5	1	
Type of psychiatric disorder, n (%)			
Psychosis	13 (21.3)	1 (1.37)	<0.001
Mood disorder	9 (14.7)	10 (13.7)	
Mania	4 (6.6)	0	
None	35 (57.4)	62 (84.93)	
No details	7	6	

* p value from χ^2 tests, Fisher's tests.

Applying logistic regression to adjust for age, gender, education and employment, the risk of having a first-degree relative affected by any psychiatric disorder was 5 times higher for cases than controls, adjusted OR: 5 (95% CI 1.6-15.2) (**Table 20**).

Table 20: OR of psychotic disorders for the presence of a history of any psychiatric or psychotic disorder in a first degree relatives.

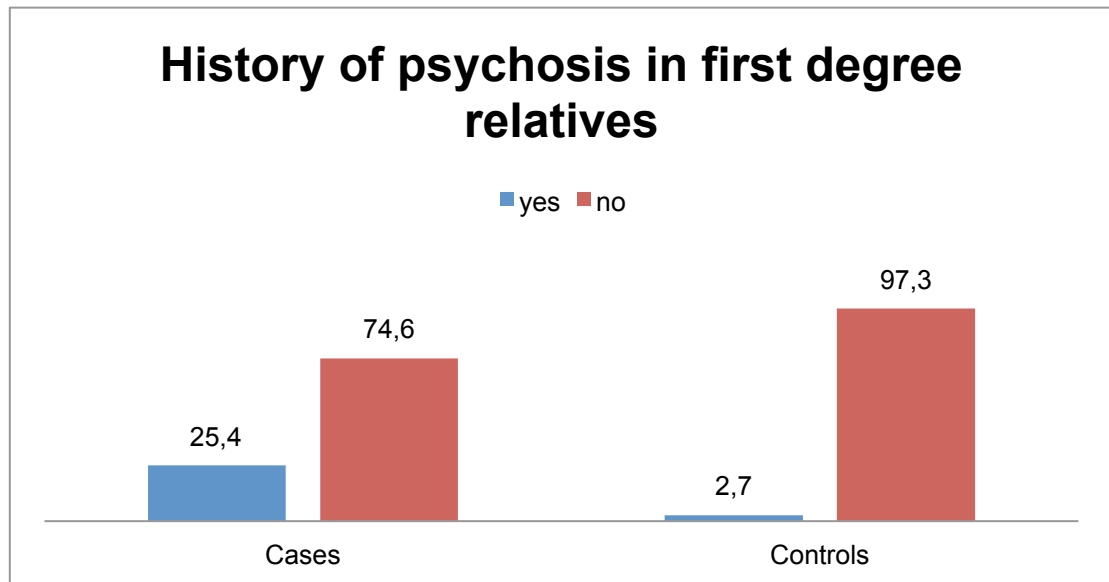
	Adj OR*	95% CI	p value
Any psychiatric disorder in first-degree relatives, n (%)	5	1.6-15.2	0.005
Psychosis in first-degree relatives, n (%)	10.3	1.7-62.2	0.01

*Adjusted for age, gender, education, employment by logistic regression.

I found a higher risk for cases to have a first-degree relative affected by a psychotic disorder with an adjusted OR of 10.3 (95% CI 1.7-62.2) (**Table 20**), however this result must be interpreted with caution because of the

wide CI due to the low proportion of controls (2.7%) having a first-degree relative affected by psychosis **Fig. 24**.

Figure 24: family history of psychotic disorders in cases and controls



5.6.3 Cannabis and the risk of psychotic disorder

Cannabis consumption is associated with an increased risk of developing a psychotic disorder (Henquet, Krabbendam et al. 2005; Moore, Zammit et al. 2007). The risk is reported to be higher when cannabis consumption starts in early adolescence (Arsenault, Cannon et al. 2002). However not all the people who smoke cannabis develop a psychotic disorder and the risk may be influenced by specific patterns of cannabis exposure such as frequency, duration and cannabis potency (Di Forti, Morgan et al., 2009). A meta-analysis reported an earlier age of psychosis onset in cannabis users (Large, Sharma, et al. 2011).

5.6.3.1.Cannabis consumption in Italy

Cannabis consumption is common in Italy. The General Population Survey (GPS-ITA 2010) was conducted in a representative sample of the general population aged 15-64 years. 22.4% of the general population had used cannabis at least once lifetime, 5.2% had used cannabis in the previous year and 3% had used cannabis in the previous month.

Cannabis use in the previous month was more common among subjects aged 15-24 years (males 16.5%, females 10.6%) and among those aged 25-34 years (males 12.5%, females 7.1%). (GPS-ITA; Dipartimento politiche antidroga, 2010). Median age of starting cannabis consumption was 18 years.

Cannabis consumption in the general population progressively increased between 2001 and 2008 and then there was a substantial decrease in 2010.

The Student population Survey (SPS-ITA) was conducted in 35.018 students aged 15-19 years in 2011. 22.1% had used cannabis at least once lifetime, 18.2% had used cannabis in the previous year and 12.9% had used cannabis in the previous month. Among students, males were more likely to have used cannabis than females in the previous year (33.9% vs 20% of females) and they were also more likely to have

smoked more than 20 times than females (30.2% vs 18.4%) (SPS –ITA 2011).

According to a survey run in 2007-2010 by the Department of Addiction in Milan, 31.7%, of a population sample aged 15-64 years reported lifetime cannabis use and 7.4% reported cannabis use in the previous month. As far as I know there are not available detailed data on Palermo population.

5.6.3.2. Aims

1. To compare pattern of cannabis consumption between cases and controls (exposure to cannabis lifetime, age at first use, duration of cannabis consumption, total number of times used, frequency of use).
2. To investigate any association of pattern of cannabis use (exposure to cannabis lifetime, age at first use, duration of cannabis consumption and total number of times used) and age at first presentation of psychosis in the group of cases.
3. To compare my results to those of the Genetic and Psychosis study (GAP) (Di Forti, Morgan et al. 2009), to detect any differences in patterns of cannabis exposure between South East London and Palermo.

5.6.3.3 Hypothesis

1. I expect no differences in terms of lifetime ever cannabis consumption in cases and controls but I expect a different pattern of consumption between the two groups: i.e. I expect cases to have an earlier age of first cannabis consumption, higher frequency and increased duration of use than controls.
2. I expect gender differences among cases and controls in patterns of using cannabis (lifetime use, frequency of use, duration of use), and I expect a higher prevalence of cannabis consumption among males as is reported in the general population.

3. In the group of cases I expect an earlier age at first presentation in those who smoke cannabis than those who do not.

I expect some similarities but also some differences in patterns of cannabis consumption in patients compared to GAP data (Di Forti, Morgan et al. 2009). For instance I expect no differences in cannabis lifetime use between cases and controls but I expect cases to have a higher frequency of cannabis use compared to controls, as in the GAP sample. I expect a lower proportion of Palermo cases and controls to have been exposed to “high potency cannabis” than in the UK reflecting the differences in the national trend of UK and Italy and the differences of the illicit drug market in London and in Palermo.

5.6.3.4 Methods

I compared patterns of cannabis use in cases and controls using where appropriate χ^2 test or Fisher exact test (cannabis use lifetime, current cannabis use, frequency of cannabis use, use before and after 15 years); Welch test and Wilcoxon (or Wilcoxon) tests were used to calculate mean age at first use and mean duration of cannabis use for cases and controls because of unequal variances. I used ANOVA to evaluate differences in the mean age of first cannabis consumption by case-control status and by gender.

Logistic regression was used to analyze the association between the pattern of cannabis use and the risk of psychosis, controlling for possible confounders. Confounders were selected as the main socio-demographic differences between cases and controls that might influence the risk of psychosis (age, gender, level of education, employment, psychiatric family history, other drug use).

5.6.3.5 Results

Table 21 summarizes patterns of cannabis use in cases and controls.

Table 21: patterns of cannabis use in cases and controls. The first row refers to all the sample of cases and controls while the following rows of the tables in light green refer only to the subgroup of cannabis smokers in cases and controls.

	Cases n, % (68)	Controls n, % (74)	p value*
Cannabis use lifetime, n (%)			
Yes	29 (44.6)	42 (56.76)	0.153
No	36 (55.4)	32 (43.2)	
No details	3	0	
Current cannabis use* (at the time of the assessment), n (%)			0.009
Yes	14 (51.85)	9 (21.4)	0.003
No ³	13 (48.15)	33 (78.5)	
No details	2	0	
Frequency of cannabis use, n (%)			0.003
Everyday	12 (44.4)	4 (10.8)	0.011
Less than everyday	15 (55.5)	33 (89.2)	
No details	2	5	
Total number of time used, n (%)			0.002
<50 times	7 (27)	22 (59.46)	0.670
>50 and over 200	19 (73)	15 (40.54)	
No details	3	5	
Age of first use, mean (s.d.)	16 (2.34)	19 (5.37)	
Mean duration cannabis, years, (sd)	7.4 (7)	6.8 (7.67)	

* p value from χ^2 tests, Fisher's tests, t test, Wilcoxon test

In Palermo sample, patients are not more likely to have smoked cannabis than controls at least once lifetime OR: 0.4 (95%CI: 0.1-1.1) as I expected; this is in line with results of Di Forti and colleagues (2009) who did not find a difference in prevalence of lifetime cannabis consumption between cases and controls OR: 0.8 (95%CI: 0.6-1.5) **table 22, Fig. 25.**

³ No current use was defined as no cannabis consumption in the previous 4 weeks as reported in the GAP study

This finding can be explained by the fact that cannabis consumption is common both in UK and in Italy.

I did not find any difference in lifetime cannabis consumption by gender both in cases ($\chi^2=1.4$, $df=1$, $p\text{-value}=0.238$, χ^2 test) and controls ($\chi^2=1.8$, $df=1$, $p\text{-value}=0.178$, χ^2 test), while in the GAP study males were more likely to have a history of cannabis use than females (Di Forti, Sallis et al., 2013).

I did not find any difference by gender either in cases and controls when I repeated the analysis considering current cannabis use at the time of the assessment.

Table 22: OR of psychotic disorders for measures of exposures to cannabis

	Adj OR*	95% CI	p value
Cannabis use lifetime, n (%)			
No	1		
yes	0.4	0.1-1.1	0.1
Being a current cannabis use at the time of the assessment)			
No	1		
Yes	5.4	1.2-24.1	0.03
Everyday cannabis consumption			
No	1		
Yes	7.5	1.9-29.7	0.004
Having smoked between 50 and over 200 times			
No	1		
Yes	5	1.5-16.4	0.007
Age at first cannabis use			
>15 years	1		
<15 years	8	2.4-27	0.001

*Adjusted for age, gender, education, family history of psychiatric disorders, other drug consumption, by logistic regression

Fig 25 shows lifetime cannabis consumption in cases and controls in the GAP sample.

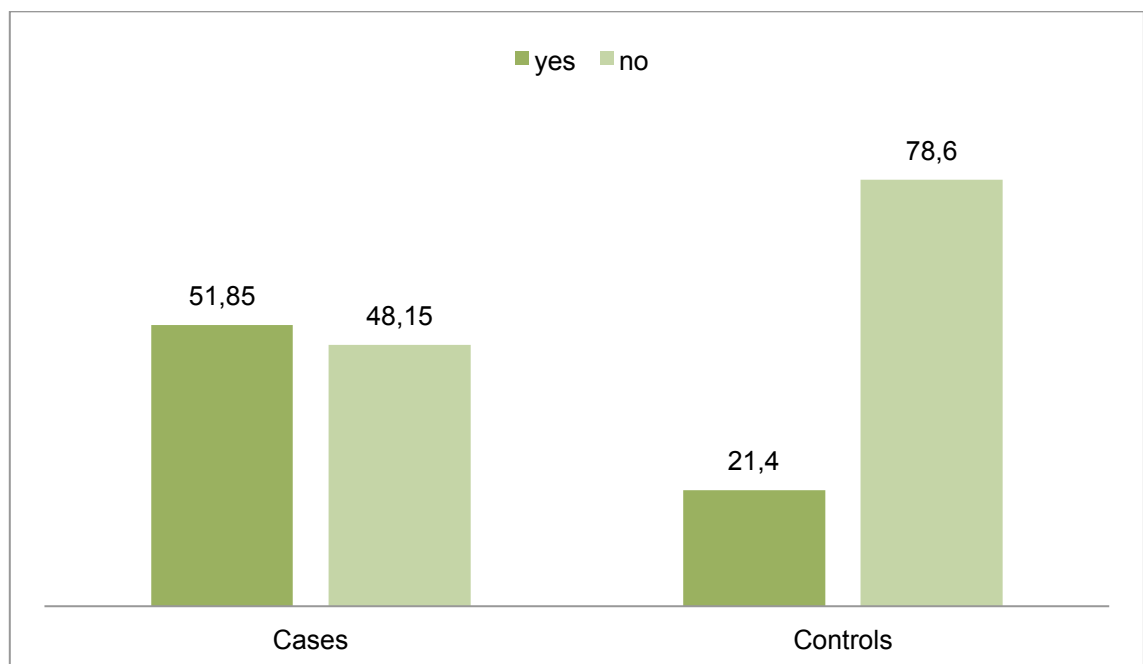
Figure 25: lifetime cannabis consumption in cases and controls in the Genetic and Psychosis study (Di Forti, Morgan 2009).

	Cases, <i>n</i> = 280 <i>n</i> (%)	Controls, <i>n</i> = 174 <i>n</i> (%)	Odds ratio (95% CI)	
			Unadjusted	Adjusted ^a
Ever used				
No	121 (43.1)	65 (37.5)	1.0	
Yes	159 (56.9)	109 (62.5)	0.8 (0.6–1.5)	
Age at first use ^b				
Under 17 years	103 (65.3)	57 (52.2)	1.7 (1.0–4.7)*	1.1 (0.8–3.4)
17 years and over	56 (34.7)	52 (47.8)	1.0	

a. Adjusted for age, gender, ethnicity, other stimulant use, level of education achieved and employment status.
b. In those who had ever used cannabis.
**P* < 0.05.

Considering all the people who ever smoked cannabis, cases were more likely than controls to currently smoke cannabis at the time of assessment meaning that they were more likely to having smoked in the previous four weeks ($\chi^2=6.8$, $df=1$, $p\text{-value}=0.017$, χ^2 test) as shown in **Fig. 26**.

Figure 26: cannabis use at the time of assessment in those cases and controls who had ever smoked cannabis.



Even after adjusting for possible confounders (age, gender, education, employment, psychiatric family history, other drugs abuse) the probability of being a current cannabis smoker was higher in cases than controls at the time of assessment; cases were over 5 times (adjusted OR: 5.4; 95%

CI: 1.2-24.1) more likely to be a smoker at the time of assessment than controls, **table 22**.

Age at first cannabis use: Mean age at first use of cannabis differed between cases and controls. Patients started cannabis consumption about 3 years earlier than controls ($t=3.1$, $df=60$, $p\text{-value}=0.002$, Welch test). The difference for mean age at first use was calculated using Welch test because of unequal variances between cases and controls.

Applying Anova, mean age at first use of cannabis was different by cases and controls ($p\text{-value}=0.020$) and by gender ($p\text{-value}=0.006$). Males tended to smoke earlier than females both in case and control groups. However there was no interaction between gender and case control status ($p\text{-value}=0.254$).

The probability of using cannabis before 17 years among cases was 4 times higher than in controls; adjusted OR: 4.2 (95% CI: 1.4-12.8) after adjusting for possible confounders by logistic regression. In the GAP sample, as shown in **Fig. 25** there was no significant difference between cases and controls in starting cannabis consumption before 17 years (Adjusted OR: 1.1; 95% CI 0.8-3.4).

Accordingly to the existing literature indicating that age 15 years old might be a critical age of first exposure (Casadio, Fernandes et al., 2011; Di Forti, Sallis et al. 2013) to cannabis use, I repeated the analysis using as a cut off “before and after 15 years”. Cases were eight times more likely to having started using cannabis before 15 years (Adj OR: 8; 95% CI 2.4-27) than controls, **table 22**.

Frequency of cannabis use: Di Forti and colleagues reported that patients were around six times more likely than the control group to use cannabis every day (Di Forti, Morgan et al. 2009) as reported in **Fig. 27**.

Figure 27: pattern of cannabis use in the GAP sample by duration, frequency and type of cannabis. (adapted with the permission from Di Forti et al., 2009).

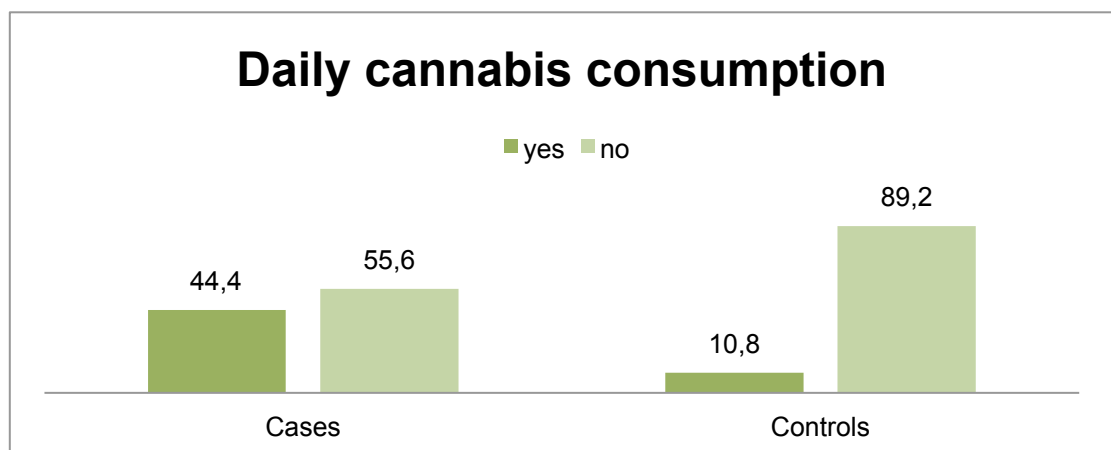
	Cases, <i>n</i> = 159 <i>n</i> (%)	Controls, <i>n</i> = 109 <i>n</i> (%)	Odds ratio (95% CI)	
			Unadjusted	Adjusted ^a
Duration of use				
0–5 years	65 (40.8)	68 (62.5)	1.0	1.0
Over 5 years	94 (59.2)	41 (37.5)	2.4 (1.2–4.7)	2.1 (0.9–8.4)*
Frequency of use				
Less than every day	37 (23.1)	73 (66.7)	1.0	1.0
Every day	122 (76.9)	36 (33.3)	6.7 (2.0–11.5)	6.4 (3.2–28.6)*
Type used				
Resin (hash) and traditional imported herbal cannabis (Δ9-THC and CBD both 1%)	34 (21.6)	68 (62.6)	1.0	1.0
Sinsemilla (skunk) (Δ9-THC 12–18%; CBD 0%)	125 (78.4)	41 (37.4)	8.1 (4.6–13.5)	6.8 (2.6–25.4)*

CBD, cannabidiol; Δ9-THC, Δ9-tetrahydrocannabinol.
a. Adjusted for age, gender, ethnicity, other stimulant use, level of education achieved and employment status.
**P* < 0.05.

In Palermo sample I grouped frequency of cannabis consumption in cannabis users in: “frequent” (meaning everyday use and more than 3 times a week), “sporadic” (meaning that the subject tried cannabis only once or twice lifetime, a few times each month and a few times each year) to see whether a difference in frequency of cannabis consumption might influence the risk of developing a psychotic disorder. Despite the lack of differences in lifetime cannabis consumption between cases and controls, cannabis users among cases were more likely to smoke more frequently than controls, adjusted OR: 4.4 (95% CI:1.08-18).

I then divided frequency of use into everyday and less than everyday as reported in **Fig. 28** to compare my data with GAP sample (Di Forti, Morgan et al 2009).

Figure 28: proportion of daily cannabis users in Palermo cases and controls among people who have ever used cannabis.



Similarly to what Di Forti and colleagues reported in their paper, in our sample cases were 7.5 times more likely to smoke cannabis everyday compared to controls ($\chi^2=9.4$, $df=1$, $p\text{-value}=0.004$, χ^2 test), adjusted OR: 7.5 (95% CI: 1.9-29.7) **table 22**. In the GAP sample, the adjusted OR was 6.4 (95% CI: 3.2-28.6). (Di Forti, Morgan et al. 2009).

Number of times used: when I considered the total number of times subjects had smoked cannabis lifetime, I found a significant difference between cases and controls. I grouped the total number of times people have smoked cannabis in two groups “once or twice-50 times” and “between 50 and 200”. Patients were more likely than controls to have used cannabis between 50 and over 200 times than controls who were more likely to have tried cannabis once or twice or between 10 and 50 times adjusted OR: 5 (95% CI: 1.5-16.4).

Duration of use: I did not find a difference in duration of use of cannabis between cases and controls. I applied Welch test for unequal variances between duration of use among cases and controls mean duration of cannabis consumption was 7.4 years for cases and 6.8 years for controls ($t=-0.3$, $df=45$, $p\text{-value}=0.785$, Welch test).

This result is similar to that of the GAP study in which the authors did not find a higher duration of cannabis consumption among cases (Di Forti, Morgan et al. 2009) as reported in **Fig. 27**.

Among cases, I did not find any significant difference in duration of cannabis use between males and females ($p\text{-value}=0.182$, Fisher test).

Potency of cannabis used: other authors have considered high potency cannabis among those patterns influencing the risk of developing psychosis (Di Forti, 2009, 2013). However in our sample only 3 cases (13%) of cases and 4 (10.8%) of controls had used high potency cannabis (sinsemilla “skunk” with high concentration of THC; Potter, Clark et al. 2008) so I had not enough power to detect any difference for the risk of developing psychosis.

The low prevalence of high potency cannabis consumption probably reflects the differences in the types of cannabis which are available in London compared to Palermo drug market. In UK in the last years, the market share of sinsemilla (skunk) has increased. According to the UK Home Office cannabis potency study 2008 herbal cannabis represented 80.8% of street cannabis confiscated by the police and 97% of that was sinsemilla; the mean concentration of THC in sinsemilla was 16.2% (Hardwick and King 2008, Home Office Cannabis Potency Study 2008). The THC concentration of marijuana grown in Italy is around 4% (Florian, L'Espresso, 2010) much lower than the 16% reported for UK by (Hardwick and King, 2008).

5.6.3.6 Age at first presentation in cases and cannabis consumption

Among cases, median age at first presentation was lower for those who had smoked cannabis in their lifetime (22 years vs 27; $z=2.4$, p -value 0.014, Wilcoxon test). I applied Wilcoxon test because of unequal variances and non-normal distribution. When I repeated the analysis for current use of cannabis at the time of the assessment, I did not find any difference in the median age at first presentation for those who were current users and those who were not (22 years vs 22.5; $z=-0.4$, p -value 0.715, Wilcoxon test).

I repeated the analysis to see whether there was an association between a higher frequency of use and the median age at first presentation of psychosis. Cases who never used cannabis were older (31.6 years) at their onset than those who smoked cannabis everyday (27 years) and less than everyday (22.5 years) ($\chi^2=7.7$, $df=2$, p -value=0.021, Kruskal-Wallis test). Applying Dunn test to compute multiple pairwise comparisons after a Kruskal-Wallis test, there was a statistical significant difference between people who smoked less than everyday and people who never smoked cannabis (p -value=0.002) while there was not any difference between people who never smoked cannabis and people who smoked everyday (p -value=0.251).

5.6.4 Drug consumption other than cannabis

5.6.4.1 Introduction

Another factor influencing the risk of psychosis is other illicit drug consumption.

Stimulants (amphetamines and methamphetamines) and cocaine may induce psychotic symptoms that may persist in those with an underlying susceptibility (familial loading for psychotic disorders) after ceasing drug consumption (Chen, Lin et al., 2005). Hallucinogens may also induce psychotic symptoms.

In Italy, the lifetime prevalence of drug consumption according to the GPS-ITA in the general population aged 15-64 years is 1.9% for hallucinogens, 2.8% for stimulants, 1.3% for heroin.

In 2011 there was a general decrease in heroin, cocaine, stimulants, hallucinogens and cannabis consumption among students.

5.6.4.2 Aims

1. To compare lifetime exposure to licit and illicit consumption between cases and controls: alcohol, tobacco, other drugs (stimulants, cocaine, hallucinogens, opiates).
2. To investigate the role of cannabis consumption as a confounder in the relation between illicit drug consumption and the risk of psychosis.

5.6.4.3 Hypothesis

I expect cases to have a higher prevalence of other drug consumption than controls.

5.6.4.4 Methods

I applied χ^2 to test for the association between being a patient and licit and illicit drug consumption.

I applied logistic regression to calculate adjusted OR for potential confounders (age, gender, education, employment, cannabis consumption).

5.6.4.5 Results

Table 23 shows the prevalence distribution of other illicit drug consumption in cases and controls. In general cases were more likely to have ever used other illicit drugs than controls.

I did not find any difference in alcohol consumption among cases and controls ($\chi^2=0.9$, $df=1$, $p\text{-value}=0.349$, χ^2 test).

Cases were over 3 times more likely to have ever tried other drugs (stimulants, hallucinogens, opiates, cocaine) than controls ($\chi^2=5.4$, $df=1$, $p\text{-value}=0.019$, χ^2 test), OR: 3.3 (95%CI: 1.16-9.32), however after adjusting lifetime exposure to other drugs for the main confounders (age, gender, education, psychiatric family history, cannabis consumption) the risk of exposure became non significant: adjusted OR: 2.3 (95% CI: 0.4-11.2).

Patients were almost 3 times more likely to smoke tobacco than controls, ($\chi^2=8.5$, $df=1$, $p\text{-value}=0.003$, χ^2 test), OR: 2.9 (95% CI:1.4-6).

After controlling tobacco use for age, gender and cannabis consumption the OR became non significant: 2.9 (95%CI: 1-8.6). It is not possible to disentangle the effect of tobacco alone on the risk of psychosis because almost all the people in the samples use cannabis together with tobacco.

Table 23: ever used other licit and illicit drugs consumption in cases and controls.

	Cases n, (%) (68)	Controls n, (%) (74)	p value*
Other drugs, n (%)			0.019
Yes	13 (22.8)	6 (8.2)	
No	44 (77.2)	67 (91.8)	
Stimulants, n (%)			0.015
Yes	12 (23)	5 (6.85)	
No	40 (77)	68 (93.15)	
No details	16	1	
Alcohol, n (%)			0.349
Yes	27 (46.55)	40 (54.8)	
No	31 (53.45)	33 (45.2)	
No details	10	1	
Tobacco, n (%)			0.003
Yes	41 (70.7)	33 (45.2)	
No	17 (29.3)	40 (54.8)	

*p value from χ^2 tests

Cases were 4 times more likely than controls to have ever used stimulants, OR: 4.1 (95%CI: 1.3-12.4) but controlling for the main confounders, stimulant use alone could not explain the risk of being a patient: adjusted OR: 1.5 (95%CI: 0.3-6.7). A larger sample is needed to detect an effect of the stimulants on psychosis.

Excluding those who never used cannabis, the risk of developing a psychotic disorder was nearly 6 times higher in those who used both cannabis and other drugs than those who just used cannabis ($\chi^2=9.8$, df=1, p-value=0.002, χ^2 test), OR: 5.8 (95%CI: 1.8-18.5) but this result is not confirmed after controlling for confounders by logistic regression OR: 2.3 (95%CI: 0.5-11.2).

5.6.5 Adult adversities

5.6.5.1 Introduction

Bebbington et al. (2004) found an excess of lifetime victimization

experiences among people affected by a psychotic disorder (Bebbington, Bhugra et al., 2004). A recent meta-analysis confirmed the association between adult life events and the increased risk of developing a psychotic disorder (Beards, Gayer-Anderson et al., 2013).

5.6.5.2 Aims

Comparing lifetime exposure to different type of adversities in cases and controls.

5.6.5.3 Hypothesis

I expect a higher prevalence of victimization experiences among cases than controls.

5.6.5.4 Methods

I used χ^2 test or Fisher exact test where appropriate to test the association between adverse life events and case control-status.

5.6.5.5 Results

Overall, I did not find an excess of adverse life events among cases as I expected, as reported in **Table 24**. However, I found a higher proportion of injury assault ($\chi^2=7.2$, $df=1$, $p\text{-value}=0.007$, χ^2 test), having been expelled from school ($p\text{-value}=0.002$, Fisher test), running away from home ($p\text{-value}<0.001$, Fisher test) and been forced into authority care ($p\text{-value}=0.013$, Fisher test) among cases. However, due to the small sample size I could not control for other variables potentially influencing the risk.

Table 24: victimization experiences in cases and controls

Victimization events lifetime, n (%)	Cases n, (%) (68)	Controls n, (%) (74)	p value*
Yes	37 (66)	38 (51.4)	0.093
No	19 (34)	36 (48.6)	
No details	12	-	
Injury/Assault			0.007
Yes	14 (25.45)	6 (8.1)	
No	41 (74.55)	68 (91.9)	
No details	13	-	
Bullying			0.068
Yes	3 (5.7)	0	
No	49 (94.2)	74 (100)	
No details	16	-	
Violence at work			>0.999
Yes	2 (3.6)	2 (2.7)	
No	53 (96.4)	72 (97.3)	
No details	13	-	
Violence at home			0.205
Yes	13 (23.6)	11 (14.9)	
No	42 (76.4)	63 (85.1)	
No details	13	-	
Sexual abuse			0.096
Yes	11 (19.6)	7 (9.5)	
No	45 (80.4)	67 (90.5)	
No details	12	-	
Expelled from school			0.002
Yes	11 (19.6)	2 (2.7)	
No	45 (80.4)	72 (97.3)	
No details	12	-	
Running away from home			<0.001
Yes	15 (26.8)	2 (2.7)	
No	41 (73.2)	72 (97.3)	
No details	12	-	
Homeless			0.184
Yes	2 (3.6)	0	
No	54 (96.4)	74 (100)	
No details	12	-	
Authority care			0.013
Yes	5 (9)	0	
No	51 (91)	74 (100)	
No details	12	-	
Children Institution			0.725
Yes	4 (7.1)	4 (5.4)	
No	52 (92.9)	70 (94.6)	
No details	12	-	

*p value from χ^2 tests, Fisher's test

5.6.6. Childhood adversities

5.6.6.1 Introduction

Recent meta-analyses report an association between exposure to childhood adversities and the risk of later developing a psychotic disorder (Matheson, Shepherd et al. 2012; Varese, Smeets et al. 2012).

There is some evidence that parental loss or permanent separation from parents (Morgan, Kirkbride et al 2006), bullying (Trotta, Di Forti et al 2013), physical (Fisher, Jones et al., 2010) and sexual abuse (Bebbington, Jonas et al. 2011) before age 16 are associated with an increased risk of developing psychosis in adulthood. However, the specificity of childhood abuse in psychotic disorders has not yet been demonstrated (Sideli, Mulè et al. 2012).

5.6.6.2 Aims

- To compare the prevalence of childhood traumatic experiences such as parental loss or separation, physical abuse, sexual abuse before age 16 between cases and controls
- To evaluate the role played by traumatic experiences in increasing the risk of developing a psychotic disorder after controlling for the main confounders.

5.6.6.3 Hypothesis

I expect cases to be more likely to have experienced some of the childhood traumatic experiences than controls.

5.6.6.4 Methods

I used χ^2 test or Fisher exact test where appropriate to test the association between life events and case control-status. Logistic regression has been used to adjust for potential confounders.

5.6.6.5 Results

Table 25 reports traumatic experiences in childhood and early adolescence (before age 16) in cases and controls. Four adverse events were reported: loss of on parents because of death, separation from one parent for more than six month for any reason, physical abuse and sexual abuse.

Table 25: traumatic experiences before 16 years in cases and controls

	Cases n (%) (68)	Controls n (%) (74)	p value
Loss of one parent (death)			
Yes	6 (10.5)	7 (9.5)	0.840
No	51 (89.5)	67 (90.5)	
No details	11	-	
Separation from one parent			0.341
Yes	13 (22.8)	12 (16.2)	0.055
No	44 (77.2)	62 (83.8)	
No details	11	-	
Physical abuse			0.008
Yes	8 (14.3)	3 (4)	0.008
No	48 (85.7)	71 (96)	
No details	12	-	
Sexual abuse			
Yes	10 (20.8)	3 (4)	0.008
No	38 (79.2)	71 (96)	
No details	16	-	

*p value from χ^2 tests, Fisher's test

I did not find any differences between cases and controls for traumatic childhood experiences of parental loss because of death ($\chi^2=0.1$, $df=1$, p-value=0.840, χ^2 test) or being separated from one parent before 17 years ($\chi^2=0.9$, $df=1$, p-value=0.341, χ^2 test), **table 25**.

Using Fisher's exact test, I found an association between being a patient and having experienced either physical abuse before 16 years (p-value=0.055, Fisher test) or sexual abuse (p-value=0.008, Fisher test) **table 25**.

Table 26: OR of psychotic disorders for adverse childhood experiences

	Adj OR*	95% CI	p value
Physical abuse			
No	1.0		
Yes	4.2	1.01-17.3	0.051
Sexual abuse			
No	1.0		
Yes	5.5	1.3-22.7	0.017

*Adjusted for age and gender by logistic regression

After adjusting for the main confounders (age, gender, family history of psychiatric disorders), the risk of having been a victim of sexual abuse among cases was 5.5 higher than controls (adjusted OR: 5.5 95% CI: 1.3-22.7) **table 26**.

The risk of being exposed to physical abuse among cases was 4.2 times higher than in controls (adjusted OR: 4 95% CI: 1.01-17.3) after adjusting for the main confounders (age, gender, family history of psychiatric disorders); however, this result must be interpreted with caution because the CI is close to 1, **table 26**.

Similarly, in the AESOP study the authors found an increased risk of being a victim of sexual abuse during childhood among cases. However, after controlling for confounders the association lost statistical significance (Fisher, Morgan et al., 2009).

These results must be interpreted with caution because of the small sample size and the proportion of missing data. Some patients (7,3%) refused to cooperate maybe because of the intimate nature of these questions.

5.7 Conclusions

Summarizing the results of the main risk factor examined in this case-control study, I found:

- 1) Family history for psychiatric disorder was significantly more common among patients than controls. Psychotic disorders were more common in first-degree relatives of patients compared to controls though this result should be interpreted with caution.
- 2) Cannabis consumption was higher among cases at the time of assessment. Patients were more likely than healthy controls to have started to smoke cannabis before 15 years, and to have a higher frequency of use.
- 3) I did not find any significant differences between cases and controls in other drug consumption after considering confounders.
- 4) I found a higher prevalence of sexual abuse and physical abuse among cases.

Chapter 6

Discussion

6.1 Introduction

In this chapter I will summarize the key finding of this thesis. I'll address methodological issues, strengths and limitations of the study, and I'll suggest how my findings might contribute to the future direction of epidemiology research into psychotic disorders.

First I'll discuss the epidemiological findings in the Palermo sample and I'll compare my results with the literature on this topic. Then I'll comment on the case-control results to examine the possible impact of certain environmental risk factors in my area.

6.2 Variation in the incidence rates of psychotic disorders

6.2.1 My Original Hypothesis

1. I expect similar incidence rates of psychoses when compared to that reported in other Italian sites (Tarricone, Mimmi et al., 2012 Lasalvia, Bonetto et al. 2014).
2. I expect to find an increased risk of psychosis in some subgroups (males and migrants).
3. I expect lower rates than those reported in UK in the AESOP study.

6.2.2 Findings

6.2.2.1 Are the incidence rates of psychosis in different centres in Italy similar?

The crude incidence rate of all psychotic disorders in Palermo is 15.9 per 100,000 per year (95% CI 13.7-18.1). The incidence of schizophrenia in Palermo is 9.6 (95% CI 7.9-11.3), and falls into the lower part of the wide range reported by McGrath and his colleagues (7.7-43 per 100,000 per year).

Previous studies carried out in Italy reported similar rates but these rates are not comparable because of different methodology.

The Bologna FEP study (BoFEP) was carried out in three mental health services of West Bologna; the methodology was similar to that in the AESOP study (inclusion and exclusion criteria, FEP diagnosis).

In Bologna the overall median IR for all psychotic disorders was 16.4 per 100,000 inhabitants per year (IQR 14.3–17.8) and it is similar to that found in Palermo. The differences in rates for other diagnostic categories are displayed in **table 27** but unfortunately Bologna and Palermo rates are not strictly comparable because I did not apply standardization in order to adjust for potential differences in the population structure between the two sites.

Table 27: crude incidence rates in Palermo and Bologna by diagnostic categories

	Crude IR* in Palermo (95% CI)	Crude IR* in Bologna (IQR)
All psychoses	15.9 (13.7-18.1)	16.4 (14.3-17.8)
Schizophrenia F20	9.6 (7.9-11.3)	7.3 (6.5–10.7)
Affective psychoses F30-33	1.5 (0.8-2.1)	1.7 (0.9–3.0)
Other psychoses F21-29	4.8 (3.6-6)	11.3 (10.1–14.2)

* Results are displayed per 100,000 persons/year

Taking into account the methodological limitations of this comparison, we can say that there are not striking differences in the rates of overall psychoses, schizophrenia and affective psychosis between Palermo and Bologna; indeed, the results are quite similar. The incidence rate of other non-affective psychoses seems to be higher in Bologna than in Palermo.

Further studies are needed to compare incidence rates in different Italian sites with a design allowing a comparison in order to detect potential differences and a different distribution of social and environmental risk factors.

The Psychosis Incident Cohort Outcome Study (PICOS) was carried out in Veneto region with a methodology close to that in the AESOP study. It is a multisite study aiming at exploring the epidemiological characteristics of psychosis in the Veneto region. It reported very recently incidence rates for psychotic disorders in Veneto (Lasalvia, Bonetto et al. 2014).

A direct comparison between the two studies was not allowed by the differences in methodology (e.g. age of first episode recruitment, inclusion of substance induced psychosis) and the rates are not comparable due to the lack of standardization to control for the differences in the two population structures. **Table 28** shows crude incidence rates in Palermo and in Veneto.

Table 28: crude incidence rates in Palermo and Veneto by diagnostic categories

	Crude IR* in Palermo (95% CI)	Crude IR* in Veneto (95% CI)
All psychoses	15.9 (13.7-18.1)	18.1 (16.7–19.7)
Schizophrenia F20	9.6 (7.9-11.3)	5.6 (4.7–6.4)
Affective psychoses F30-33	1.5 (0.8-2.1)	3.8 (3.1–4.6)
Other psychoses F21-29	4.8 (3.6-6)	14.3 (13.0–15.7)

* Results are displayed per 100,000 persons/year

It is possible to have just a general idea of the similarities in incidence rates between the two sites taking into account the fact that the Veneto rates come from different sites both urban and rural.

Overall rates of psychosis in Veneto is 18.1 per 100,000 per year; rates of affective psychosis is 3.8 per 100,000 per year which is higher than in Palermo but lower than in the AESOP study. Previous studies in Verona reported a similar rate of affective psychoses: 4 per 100,000 per year (Tansella, Balestrieri et al. 1991).

In the Veneto sample, there is not any significant difference in gender composition of cases while in Palermo males are overrepresented. The different gender distribution or the age of population may account for the rate differences in affective psychosis.

6.2.2.2 Is the incidence of psychosis in Palermo the same in all subgroups? Is there variation by gender and migrant status?

Male gender has been associated with an increased risk of schizophrenia.

In the Palermo sample there is an increased risk for all psychoses IRR: 1.7 (95% CI 1.3-2.2) and for schizophrenia IRR: 2 (95% CI 1.4-2.9), in males. This result is in line with previous FEP studies reporting an increased risk of developing psychoses and schizophrenia in males.

In the AESOP study males had an increased risk of developing any psychotic disorder: IRR: 1.5 (95% CI 1.3-1.8). The risk was significantly higher in males than females for other non affective psychosis IRR: 1.8 (95% CI 1.4-2.2) and for schizophrenia IRR:2.4 (95% CI 1.8-3.2) but not for affective psychoses. (Kirkbride, Fearon et al. 2006). In Bologna males had a higher risk of overall psychoses IRR:1.4 (95% CI 1.08-1.7) and schizophrenia IRR:2.1 (95% CI 1.7-2.6); the different risk by gender was evident in young people but after 35-45 the difference disappeared (Tarricone, Mimmi et al 2012). In the PICOS study no differences by gender for overall psychoses were observed except for schizophrenia,

males had an increased risk of compared to females IRR: 1.7 (95% CI 1.2–2.3) (Lasalvia, Bonetto et al 2014).

I did not find any gender differences for the risk for affective psychoses and other non affective psychoses; the lack of difference in the incidence of affective psychoses in men and women has been also reported in UK in the AESOP study (Kirkbride, Fearon et al. 2006) and in a systematic review on the incidence and prevalence of schizophrenia and other psychoses in England (Kirkbride, Errazuriz 2012).

Migration in Palermo is a relatively recent phenomenon, and it is less widespread than in other cities especially when compared to London UK and the Northern Italian cities. This can be explained by the fact that Palermo, the main city of Sicily, is among the regions in Italy with the highest rate of unemployment (19.2% in 2012, Istat); so it does not represent a very attractive destination for people who are looking for a job.

The overall earlier age at first presentation of migrants might depend on the small proportion, among migrants, of people with a diagnosis of other non-affective psychoses (4 cases over 21) which usually includes disorders developing later in life. It also might be that people of an older age go back to their country of origin especially when they become ill.

Migration status has been associated to an increased risk of developing a psychotic disorder (Cantor-Graae and Selten, 2005). In Palermo sample, migrants have a near 3 fold increased risk of developing all psychoses when compared to native-born Italians. The risk of schizophrenia was 4 times higher in migrants. These results were controlled by age and gender because migrants tend to be younger than native-born Italians.

No increased risk has been found by migration for other non-affective psychoses and it was not possible to evaluate the role of migration on affective psychoses because of the absence of affective psychoses among migrants. The sample of migrants was very small and a larger sample would be needed to detect the effect on migration on this subgroup.

My findings are similar to those in the BoFEP study. Tarricone and colleagues (2012) found a higher risk of developing psychoses in migrants compared to natives: IRR: 2.5 (95% CI 2.1-2.9) and an increased risk of schizophrenia: IRR: 3.4 (95% CI 3-3.8). Despite some differences in the methodology, the categories “migrant” and “natives” applied for cases and population in the denominator overlap in both Palermo and BoFEP study.

An increased risk of overall psychosis in migrants: IRR: 2.3 (95% CI 1.8-2.7) was also reported by the PICOS study in Veneto (Lasalvia, Bonetto et al. 2014).

The reason why migration is associated to higher incidence of psychosis is not completely clarified yet. The increased risk may be related to social exclusion, discrimination and isolation (Boydell, van Os, et al. 2001; Veling, Selten et al. 2006). Unfortunately, the present study did not explore such variables.

The AESOP study reported higher risk of psychoses in ethnic minorities, especially schizophrenia and mania in Black Caribbean and Black African ethnic minorities compared to the White British (Fearon, Kikbride et al. 2006).

In the Palermo sample, I did not have enough power to detect differences among ethnic minorities; migrants have been divided in broad categories which certainly do not reflect the complexity of cultural and genetic differences.

Only 10% of cases were born outside Italy. They were equally distributed by continent of origin (7 from Asia, 7 from Africa and 7 from other European countries). However they came from very different places of each continent and they belonged to different ethnicities. For example among those coming from Africa there were people from Tunisia and Morocco which are geographically very close to Sicily and people from Ghana which is different from the ethnic and cultural point of view with respect to people coming from Northern Africa.

The small numbers of cases among non-Italian born people did not allow me to differentiate them according to ethnicity and I preferred to group people by migration status assuming that being a migrant in a foreign country represents a risk factor for the development of a psychotic disorder.

The term migrant used in this thesis is different from the concept of ethnic minorities used in the AESOP study. Migrant, according to the Italian census, refers to people who were born outside Italy while in the AESOP study belonging to an ethnic minority, does not necessarily mean that one was born outside UK.

6.2.2.3 Incidence rates of psychosis in Palermo and in the AESOP study: is the risk of developing psychosis the same in Sicily and UK?

When compared to the AESOP study, the distribution of psychotic disorders in Palermo is quite different.

In AESOP the sample comprised of 45% cases of schizophrenia and 26% other non affective psychoses) while in Palermo schizophrenia represented 60% of all psychoses.

In AESOP the proportion of affective psychoses is higher than in Palermo (29% versus 9.3%).

In both the Palermo and AESOP studies the median age at first presentation of all psychoses was significantly lower in men than women (26.5 and 27 respectively). This is in line with previous studies (Castle, Sham et al. 1998; Hafner 2003; Eranti, MacCabe et al., 2013).

As shown in **fig. 10** and **11** in chapter 4, males have higher rates of all psychotic disorders till 30-34 years both in Palermo and in AESOP with a similar trend. This may be explained by the higher risk of schizophrenia in earlier stage of life in men compared to other non-affective and affective psychoses. The differences by gender tend to disappear with aging.

When looking at the standardized incidence rates in Palermo, obtained by applying AESOP specific incidence rates to Palermo population, there is

a difference for overall psychotic disorders. After standardizing for age and gender, the incidence in Palermo is 17.5 per 100,000 per year (95% CI 15.2-20.1) compared to 27.1 per 100,000 per year (95% CI 24.4-30) in AESOP with a reciprocal of the SMR of 1.5. So people in London and Nottingham have a higher risk of developing a psychotic disorder compared to Palermo.

However, I did not find any difference in the risk of developing schizophrenia or other non-affective psychoses in Palermo and AESOP so the excess of psychoses in UK may be due to the higher risk of developing affective psychoses in UK. The risk of developing depression with psychotic features and mania is 4.5 fold higher in London and Nottingham than in Palermo and this result raises the question whether this is a true difference or whether there is a methodological bias.

Then I stratified the risk of psychosis for migration status to see whether the differences in rates found between Palermo and AESOP were due to differences between native groups or to the migrant groups.

I did not find any difference in the risk of overall psychosis between migrants in Palermo and UK. The difference of overall psychosis remained higher in British natives compared to Palermo natives-Italian because of an excess of affective psychoses in native British compared to Italians.

The systematic review by Kirkbride and colleagues (Kirkbride, Errazuriz 2012) reported a pooled annual incidence of 12 per 100,000 persons year for affective psychoses in UK. In London and Nottingham, the rate for affective psychosis was 7.3 per 100,000 per year (95% CI 5.9-8.9). In Palermo it was 1.6 (95% CI 1-2.5). However, previous studies in Italy reported a lower rate of affective psychoses compared to other sites in Europe (Tansella, Balestrieri et al. 1991); the authors put forward the hypothesis that affective psychoses were more likely to be treated by general practitioners or by neurologists in Italy (Bebbington and Tansella, 1989) so it might be that a proportion of those with affective psychosis

might have been treated privately or by family doctors and not reported to the study.

Furthermore, despite the effort to the same diagnostic procedures as in AESOP it could have been that there are transnational differences in the way in which a diagnosis of affective psychosis is made in UK and in Palermo.

One of the reasons for the difference of psychoses rates between the two sites could have been the different proportion of migrants in the samples. Standardization was applied also for migration to take into account the differences in the population structure between Palermo and AESOP. The risk remained slightly higher in UK for overall psychoses: SMR: 0.8 (95% CI 0.7-0.9) and affective psychoses SMR:0.3 (95% CI 0.2-0.4) but the risk of schizophrenia became higher in Palermo than London and Nottingham (SMR: 1.3 (95% CI 1.1-1.6).

There was not any significant difference in the rate of other non-affective psychosis in Palermo and in AESOP. The absence of affective psychoses among migrants might be due to cultural and linguistic barriers precluding to get some psychopathological feature in migrants, with an overestimation of schizophrenia versus affective or other non-affective psychoses.

I excluded second generation migrants from the AESOP sample as explained in details the methods chapter because such a classification is not available in the Italian census. This was a pity since, as reported by literature, they may be particularly vulnerable to psychosis risk (Cantor-Grae and Selten, 2005).

Migration alone cannot explain the difference in risk observed between sites. Probably other factors may play a role in increasing the risk of psychosis in UK, however further studies are needed to clarify these findings.

The lower rates of affective psychoses in Palermo compared to AESOP raises some questions. Is this a true difference or it is due to a bias in the

screening of affective psychoses or in the diagnosis of these disorders? If we detect a true difference how can we explain this variation?

First, Palermo study has been designed with a very similar methodology to AESOP on purpose, to try to detect differences among sites. So the screening procedure and the assessment of diagnoses, was similar. A leakage study was carried out to detect any missing cases, so it is unlikely that I have missed so many affective psychotic cases to determine such a difference in rates.

However, it might be that people with affective psychosis do not look for psychiatric care in public mental health services. They may search for help from private psychiatrists; unfortunately there are no published data on the pathway to care in Sicily for different psychiatric disorders.

Second, crude rates of affective psychoses in Palermo and in Bologna were similar (1.5 in Palermo and 1.7 in Bologna per 100,000 per year) even though the lack of standardization does not allow one to make a proper comparison.

Another hypothesis is that there might be a protective factor in South Europe against affective psychoses, but if so, what can it be?

I can speculate that some factors known as exerting a protective function in mood disorder play also role in affective psychoses.

Is there a North-South gradient in the risk of psychotic disorder? Other diseases such as multiple sclerosis, certain cancers (prostate, breast and colorectal), insulin-dependent diabetes mellitus and schizophrenia have been linked to hypovitaminosis D (McGrath, 2011); prevalence of multiple sclerosis shows a latitude gradient (Simpson, Blizzard et al. 2011). McGrath (McGrath, 1999) made the hypothesis that low maternal vitamin D was associated with an increased risk of developing schizophrenia and recently a mini meta-analysis reported a decrease in vitamin D levels in patients with psychosis (McGrath, Eyles et al. 2010; Belvederi Murri, Respino et al. 2013; Crews, Lally et al. 2013). Casual sunlight exposure is the major source of vitamin D (Holick, 1990). Is it possible that affective psychoses are influenced by sunlight exposure? Lack of sunlight and

reduced serotonin levels are associated with seasonal affective disorder. Patients affected by seasonal affective disorder (SAD) develop depression during the autumn or winter; symptoms remit in the spring or summer and the exposure to light provide benefits (Partonen and Lönnqvist, 1998). It is more common in countries that are far away from the equator during the winter months.

To answer these questions further studies are needed to:

1. compare affective psychosis incidence rates among different Italian sites
2. compare Italian rates with northern European countries ones.

6.2.2.4 Do social factors play a role in explaining the difference in rates of affective psychoses between Palermo and UK?

Another possible explanation for the lower incidence of affective psychoses in Palermo might be the differences in social factors and family structure in Italy and in UK.

People affected by psychotic disorders often experience marked social disadvantage in adult life (Morgan, Kirkbride et al. 2008), they are more likely to live alone, be unemployed, and have few close relationships. In the AESOP study, cases were more likely to be socially disadvantaged and isolated than healthy controls (Morgan, Kirkbride et al. 2008).

In the Genetic and Psychosis study (GAP) subjects suffering from affective psychoses were significantly more likely to report adult social disadvantage than controls although social disadvantage was more pronounced for patients affected by non-affective psychoses (Stilo, Di Forti et al., 2012).

Some authors have suggested that living alone is associated with an increased risk of mental health problems, higher rates of consumption of psychotropic drugs, and a higher risk of suicide compared to living with other persons in the same household (e.g. Pulkki-Råback, Kivimäki et al. 2012). The same authors reported increased antidepressant consumption associated with living alone (Pulkki-Råback, Kivimäki et al. 2012).

Higher suicide rates have been reported in people living alone in London (Sainsbury, 1955); living alone may represent a risk factor for self-harm behaviours (Haw and Hawton, 2011).

In the Palermo sample socio demographic variables were collected using the same instruments in Palermo and AESOP (the Medical Research Council Sociodemographic Schedule, MRC).

94.6 % of the patients in Palermo sample lived with someone else at the time of onset; 61% lived with their parents and 18.7% with their own family (with partner or partner and children); only 3.1 % of cases lived alone.

In the AESOP study the proportion of people living alone was much higher 43.3% (Morgan, Kirkbride et al. 2008). This represents a potentially important difference between Palermo and UK although I did not make a direct comparison of the two samples.

There were not such big differences in other indicators of social disadvantage; the proportion of unemployment people in Palermo (54%) and AESOP (53%) were similar and also the relationship status: 72.7% of cases in Palermo and 71.3% in AESOP were single.

It might be that living with parents or with the family exerts a protective role against the development of affective psychoses but there are at least two issues about that. First, living alone and other markers of social disadvantage have been reported to be important for psychosis and for schizophrenia, but schizophrenia rates are not lower in Palermo compared to UK. Second, it would be strange if a single social factor explained the rates differences. It is more probable that multiple environmental factors such as social isolation, urbanicity, migration and substance consumption interact with biological and genetic factors in modulating the risk of psychoses. Multi-centric epidemiological and case controls studies are needed to describe incidence patterns in Europe and to further explore the role of putative risk factors for psychotic disorders.

6.3 Strengths of the incidence study

Most of the knowledge about epidemiology and risk factors associated with first episode psychoses comes from research in Northern Europe. This epidemiological study is the first ever carried out in Sicily and one of the few from Southern Europe. It is an incidence and case control first-episode study including all potential cases who presented to services within the catchment area with a broad definition of psychosis. Thus, it may contribute to increasing the awareness of similarities and differences in terms of incidence across Europe and in Italy.

The methodology is similar to that in the AESOP study both in the design of the study and in the assessments; this allowed me to make comparisons of the incidence rates in Palermo and UK applying indirect standardization to obtain true differences between sites. Similar methods have been applied for the Bologna and Veneto epidemiological studies so one future direction may be to compare rates among the three sites applying standardization to obtain reliable and comparable results. Identifying differences in incidence rates of psychotic disorders in Italy and in Europe may lead to further clues on the different impact of risk factors.

The catchment area was well defined and included all the mental health services of the city. I used 2011 census data to obtain the population denominator to allow comparability with other future epidemiological studies.

The accuracy of denominator has been confirmed by the Italian Post Enumeration Survey. The aim of the survey, which took place from April to July 2012, was to estimate the number of individuals really and usually resident at the reference time of the 15th General Census of Population and Housing (October 9th, 2011) and the coverage rate, defined as the ratio between the number of individuals found at Census and the number of individuals really resident. At the national level, the under coverage is 1.07% that is the legal population of the

Census under enumerated for approximately 642,000 individuals (ISTAT, 2015).

The screening procedure of cases involved both inpatient and outpatient units. If a case was missed when admitted in the hospital, it is unlikely that we would have missed him/her also afterwards because s/he would have been referred to the outpatient units, which were screened regularly. Further, a leakage study was conducted to avoid missing cases and the basic socio-demographic information needed to calculate incidence was collected.

The diagnosis was based on operational criteria and it was reached by consensus.

The comparison of incidence rates between Palermo and AESOP study was done recalculating specific AESOP incidence rates after excluding people belonging to UK born ethnic minorities in order to make the two samples comparable. In the Palermo sample, I had a dichotomous variable distinguishing people who were native Italians and people who were migrants (non-Italy born). The AESOP sample originally included White British, ethnic minorities who born abroad, and ethnic minorities who born in UK; it would have been incorrect to consider the latter as the native category and, at the same time, it would have been incorrect to include them in migrants; so the analyses were performed without those people to allow an accurate comparison.

The knowledge of the epidemiology of psychosis and the prevalence of environmental risk factors in Palermo area will help mental health services to plan adequate prevention and clinical strategies to implement the treatment of psychotic disorders.

6.4 Limitations of the incidence study

One of the main concerns in an epidemiological study is to be sure about the accuracy of numerator and the denominator.

For the numerator the issue is being sure of having identified all cases affected by a psychotic episode in the period considered. In the Palermo sample, accuracy of the data collected relied on the weekly screening at the mental health services and clinical notes consultation. After the end of the data collection, I did a leakage study to identify any missing cases; in this way the main socio-demographic and clinical features have been collected.

One reason for missing cases could have been that a certain number of people in the population might have asked private psychiatrists for psychiatric care because of the fear of being stigmatized; however, since patients who were prescribed new antipsychotics had to pay a lot till 2012, to buy medication without a special receipt released only by the public mental health services.

As mentioned in Chapter 3, I did not have the chance to reach patients who looked for care in private individual settings. While all the private psychiatric hospitals in the catchment area have been covered; it is not possible to exclude the possibility that I missed some of those patients treated exclusively by private psychiatrists, however, it would be unlikely that I have missed a great proportion of patients; it is more likely that most of the people affected by psychosis would seek care both in private and in public hospitals because a number of reasons.

First, as already explained, during the study period, antipsychotic medications were too expensive unless prescribed by a public mental health service. Second, people affected by a first episode of psychosis have a high probability to be admitted to hospital at least once in a three-year period; although specific regional data are not available, the international literature data report high hospitalization rates (80%) for people affected by a first episode of psychosis (Sipos, Harrison et al. 2002).

Thus, although I can't exclude that a proportion of patients have been missed, but I think that the risk of underestimation of the numerator is minimal.

Another source of missing cases could have been admission outside the catchment area. It may have happened that some patients at their first episode could have been admitted outside the catchment area. This is because people admitted at the emergency room of one of the hospitals within the catchment area for an acute episode of psychosis, might then be admitted to another hospital outside Palermo or even outside the province, because of the lack of beds. However, after the admission, such patients would have been referred back to the outpatient unit they belonged to, according to their residence area. So it would be unlikely to have missed patients at their first episode unless they had just a single episode and they immediately totally recovered.

Because of geographical reasons (Sicily is an island), it is very unlikely that people affected by a first episode of psychosis are treated outside the region. Of course we might have missed people who are temporary outside the region for studying or for work reasons. However, if they are resident in Palermo it is unlikely that we have missed them in a three-year period.

This study relies on treated cases of psychosis so it is possible that incidence rates are influenced by the pattern of access to healthcare services; however, I tried to reduce any possible underestimation of incidence cases by involving all the inpatient and outpatient mental health services and private hospitals of Palermo.

Migrants have high rates and rate ratios with wide confidence intervals. This might be due to an underestimation of the population of migrants in the census. About 500,000 over 642,000 individuals who were missing in the enumeration census at the national level, were individuals with foreign citizenship; this represents a signal of the difficulty in detecting people coming from another country (ISTAT, 2015); however, as previously reported, the national undercover is about 1% so it is unlikely that this would have affect the incidence rates in migrants.

Another hypothesis would be that Italian born cases have been underestimated, however this seems unlikely since migrants may have

more difficulties in accessing mental health services and more complex pathways to care than the general native population (Tarricone, Stivanello et al., 2012).

With respect to the numerator, it is possible that I have missed a proportion of migrant people affected by psychosis but who did not have the chance/wish to look for psychiatric care. However, having underestimated the number of migrant people affected by psychosis would have raised the rates rather than lower them.

Since this study was not supported by any special grant, the lack of funds did not allow me to follow-up first episode cases. In psychiatry, clinical expression may vary across time. It would have been valuable to had the chance of confirming the diagnosis 12 months after the onset. However, other studies in the literature reported incidence data, based on baseline analyses (Kirkbride, Fearon et al 2006; Tarricone, Mimmi et al 2012).

The denominator has been calculated using the most reliable source of national statistical information. There could, however, be an underestimation of migrants both in the denominator (because the official census does not take into account illegal migrants) and of the numerator because it is likely that the access to mental is less easy for migrants who are less aware about the way to access health services.

Palermo and AESOP epidemiological data were collected in different time periods: Palermo incidence data were collected between 2008-2011 while AESOP data between 1997-1999. However, UK incidence rates of psychoses have tended to be stable over time as reported by a recent meta-analyses; it has been reported an increased rate of schizophrenia between 1965 and 1997 in London (possibly due to increases in the proportion of ethnic minority populations); by contrast, data from studies in Nottingham found no evidence of an increase in schizophrenia over roughly the same time period or reported a decrease; however, the authors found no evidence to support an overall change in the incidence of psychotic disorder over time in UK (Kirkbride, Errazuriz et al., 2012).

Palermo and Bologna rates could not be compared applying standardization because of the lack of specific incidence rates for the same age bands in Bologna. So I just compared crude rates which do not take into account any differences in the population structure between the two sites. Bologna has a higher proportion of migrants 12.7% (compared to the 4% in Palermo) and they are both external (from other countries) and internal migrants (people coming from other regions in Italy). I did not compare Palermo and Veneto rates standardizing for the same population because of methodological differences.

Another possible limitation of the study is that age at first contact with psychiatric services has been used as a proxy for the age of onset. I am aware that it is not a precise measure of the actual onset, but because of the course of psychotic disorders that are often subtle in their onset, it is not easy to indicate the precise date the disorder appeared. However previous studies have considered the date of first contact with services as a proxy for date of onset of psychotic disorders (Sartorius, Jablensky et al 1989; Eranti, Maccabe et al 2013).

6.5 Risk factors for psychosis in Palermo

6.5.1 Original Hypothesis

1. I expected a higher prevalence of psychiatric and psychotic disorders in first-degree relatives of cases when compared to relatives of healthy controls. I expected cases with a first-degree relative affected by a psychotic disorder to have an earlier age at first presentation than those without.
2. I expected cases to report a higher exposure to cannabis than healthy controls. I expected a different pattern of consumption (frequency, duration, age at first use) between the two groups. I expected gender differences among cases and controls in patterns of using cannabis (lifetime use, frequency of use, duration of use), I expected a higher prevalence of cannabis consumption among males as is reported in

the general population. In the group of cases I expected an earlier age at first presentation in those who smoke cannabis than those who do not.

3. I expected a prevalence of other illicit drug consumption in cases than healthy controls. I expected an excess of childhood traumatic experiences in cases compared to controls and I expected some of the adult life events to be more common in the group of cases than controls.

6.5.2 Findings

6.5.2.1 Family history of psychiatric disorders and risk of schizophrenia

Byrne and colleagues reported an increased risk of schizophrenia in people with a family history of all psychiatric disorders (and with a family history of suicide (Byrne, Agerbo et al. 2002)). In the Palermo sample, 44% of patients had a first-degree relative affected by a major psychiatric disorder (mood disorder or psychosis) compared to 15% of healthy controls. Cases were 5 times more likely to have a first-degree relative affected by any psychiatric disorder. Due to the small sample size I could not explore the differences in the risk by diagnostic category.

If cases had an excess of first-degree relatives (e.g. having more siblings than controls), this might have influenced the differences between cases and controls; since the total number of first-degree relatives in cases and controls was not available, I could not control for that. However, it is unlikely that the difference in the risk between cases and controls is explained by this.

It would be interesting to see whether the increased risk due to familial load is specific for schizophrenia or if it plays a role also in affective and other non-affective psychoses in a larger sample. I also found a higher risk for cases to have a first-degree relative affected by a psychotic disorder compared to healthy controls but this result must be

interpreted with caution due to the small proportion of controls with a first-degree relative affected by psychosis and the wide confidence interval. As reported by other studies (Suvisaari, Haukka et al. 1998; Byrne, Agerbo et al. 2002) my results support the association between having a first-degree relative affected by a psychiatric disorder and an earlier onset of psychosis compared to those without a family history of psychiatric disorders.

6.5.2.2 Cannabis use and the risk of psychosis

Cannabis exposure is reported to increase the risk of developing schizophrenia and psychosis (Henquet and Murray 2005; Moore, Zammit et al., 2007). In the Palermo sample lifetime cannabis exposure was similar in patients and in healthy controls, as in the GAP study where the authors did not find any difference in lifetime prevalence of cannabis use between patients and controls.

This might be explained by the high prevalence of lifetime cannabis use among young people in South London and in Italy. However, lifetime cannabis use does not say much about the extent of exposure to cannabis. It is likely that some people only tried cannabis a few times in their life.

A more significant index of cannabis exposure is cannabis consumption before the onset; in this work I considered “cannabis consumption at the time of assessment”. People were considered as non-cannabis users at the time of the assessment if they had not used any cannabis in the previous four weeks. Excluding cases and controls who never smoked cannabis, I found that cases were 5 times more likely than controls to be current users at the time of assessment, adjusted OR: 5.4 (95% CI: 1.2-24.1), but again this does not say much about the amount of cannabis exposure and only suggests that patients may have smoked more recently than healthy controls.

I did not find any difference in cannabis use (lifetime and current use), thus disconfirming my expectation of gender differences both in cases

and controls, while in the GAP study there was a higher prevalence in cannabis consumption in males among cases ($p < 0.01$) (Di Forti, Sallis et al., 2013).

Moore and colleagues (2007) reported a dose-response relationship between cannabis consumption and risk of psychotic disorder. Frequency is one of the parameters of cannabis consumption that can modulate the risk of psychosis (Di Forti, Sallis et al., 2009).

In the Palermo sample, frequency of cannabis use was significantly higher in cases after controlling for the main confounders (age, gender, education, employment, psychiatric family history, other illicit drugs abuse).

Frequency of cannabis consumption was classified as “frequent” (grouping everyday use and more than 3 times a week), or as “sporadic” (only once or twice lifetime, a few times each month and a few times each year cannabis consumption). After controlling for the main confounders, cannabis users among cases were four times more likely to be frequent users than controls who tended to use cannabis in a sporadic way.

I also examined daily use and I found that cases were 7.5 times more likely to smoke cannabis everyday compared to controls; this result is in line with the GAP study findings. In the GAP study the strongest predictor of case-control status was daily use of high potency cannabis (Di Forti, Morgan et al. 2009). I did not have the chance to measure the effect of low and high potency kinds of cannabis due to the low exposure in Palermo sample to high potency cannabis (only 3 cases and 4 controls had ever tried high potency cannabis).

The results in this sample confirm the role of frequency of use in increasing the risk of developing psychotic disorder.

No differences were found in the duration in years of cannabis use between cases and controls; this result diverges from the GAP study in which the authors found a higher duration of cannabis consumption among cases (Di Forti, Morgan et al. 2009) as reported in **Fig. 28**,

however, after adjusting for the confounders the difference did not reach the statistical significance because the confidence interval includes 1.

Arsenault and colleagues (2002) reported an association between earlier age at first cannabis use and a higher risk of schizophrenia. In Palermo sample, cases started to smoke cannabis significantly earlier than controls; cases were more likely than healthy controls to have started cannabis consumption before the age of 15 years and to smoke more frequently. This is interesting because some authors suggested that cannabis consumption may impact on brain development, and that early adolescence may, therefore, be a critical period for effects that do not occur when exposure begins later (Wilson, Mathew et al. 2014).

These results confirm the different pattern of cannabis consumption in people affected by psychosis and this may lead to consider cannabis as a contributing factor in the aetiology of psychotic disorders. I controlled for the role of possible confounders as socio-demographic (age, gender, level of education and employment) and other environmental risk factors (other drug use and stimulant use). Demonstrating that frequency of use and early cannabis consumption is associated to an increased risk of psychosis may have relevance in public health prevention strategies and in organizing specific educational programs with adolescents.

Psychotic patients with a history of cannabis use have an earlier age at first presentation of psychosis than those without such a history by almost 3 years (Large, Sharma et al. 2011; Donoghue, Doody et al., 2014).

In Palermo sample, mean age at first presentation in cases was earlier for those who had smoked cannabis lifetime (24.2 years vs 31.6) but the difference in mean age at first presentation was not significant any longer when I repeated the analysis for current users at the time of the assessment.

My results partially confirm the observation of the GAP study: cases who never used cannabis were significantly older at their onset than those who smoked cannabis.

In Palermo sample, frequency of cannabis consumption does not seem to have an effect on the earlier onset of psychosis. This result differs from the GAP study that reported an earlier onset of psychosis for those who smoke cannabis daily and especially high potency cannabis (Di Forti, Morgan et al. 2009). In Palermo sample however I could not explore the role of cannabis potency in the earlier onset of psychosis because of lack of detailed data, as explained in chapter five.

6.5.2.3 Other risk factors for psychosis

I also investigated the role of other environmental risk factors associated to psychosis as illicit and licit drug consumption, adverse experiences and childhood traumatic events.

Cases were more likely than controls to report other illicit drug consumption such as stimulant and tobacco use. However, exposure to tobacco and stimulants did not increase the risk of psychosis after adjusting for potential confounders (age, gender, education, employment, psychiatric family history, cannabis consumption) possibly because of the small sample size. I also found a higher risk of developing psychosis in those who ever used both cannabis and other drugs compared to those who only used cannabis but this result was not significant after controlling for the confounders. These results should be replicated in a larger case-control sample.

Some lifetime victimization experiences as having been injured or assaulted, having been expelled from school, running away from home and having been forced into authority care were more represented among cases than controls. However, I could not adjust the results by the main confounders (age, gender, education and employment) because of the small proportion of people exposed to each event.

The role and the specificity of childhood victimization experiences is still controversial. In the Palermo sample among childhood traumatic experiences there was not any difference between cases and controls in loss or separation from parents.

Physical and sexual abuses were significantly more common in cases. The risk of reporting sexual abuse during childhood and early adolescence among cases was 5.5 higher than among controls. The risk of being exposed to physical abuse among cases was 4.2 times higher than in controls (even though the result must be interpreted with caution because the CI is close to 1).

However, only a small proportion of cases and controls report physical or sexual abuse so this result must be interpreted with caution and replicated in a larger case control study. Similarly, in the AESOP study the authors found an increased risk of being a victim of sexual abuse during childhood among cases. However, after controlling for confounders the association lost statistical significance (Fisher, Morgan et al., 2009).

6.6 Strengths and limitation of the case-control study

The case control study is suitable for rare diseases as psychosis because the exposures are collected retrospectively. It allows to compare the prevalence of certain risk factors in a group of people affected by the disorder and a group of healthy controls. Unfortunately, only 33.3% of 204 patients completed the whole assessment. 136 cases identified for the incidence analysis were not enrolled in the study either because they refused to be interviewed (53%) or because they had been screened and identified retrospectively (47%) by the leakage study.

When cases have been identified retrospectively and it was not possible to contact them (either because they refused to be assessed or because they were not in contact any longer with the mental health services), data were collected from clinical notes. So it was not possible to obtain quantitative and sometimes qualitative details on their substance abuse, family history of psychotic disorders, PANSS scores. However it was still possible to collect the basic socio-demographic information and the symptoms of psychosis and this allowed me to make a proper diagnosis and to use the core information for epidemiological purposes.

Case-control designs are prone to selection bias of both cases and controls.

Bias selection of cases may have occurred because only one third of the patients identified for the incidence study were then recruited and assessed for the case-control analysis; it may be argued that they are not representative of the population of cases. However, as discussed in Chapter 3, when the group of recruited cases were compared to those who have not been recruited, no significant differences were found in several variables that might have affected the measure of the association with the risk factors under investigation. There were no differences in terms of gender, ethnicity migration, level of education; recruited cases tend to be older than non-recruited ones and there was a higher proportion of schizophrenia diagnosis among the recruited people. The implication of this difference is that the risk factors identified in cases might be more specific for schizophrenic patients than for other psychoses.

It might be argued that symptom severity might have biased the selection of cases excluding for example those with a more severe illness.

Unfortunately a direct measure of symptoms severity was not available for non-recruited cases since PANSS has only been administered to cases who were assessed by interviews; however I can infer that there were not substantial differences in symptoms severity between the recruited and the not recruited group by indirect clues.

First, not recruited and recruited cases had the same probability to have been identified in private and public hospitals (Pearson $\chi^2=0.0025$, $df=1$, $p=0.960$). People admitted to private hospitals are often less acute than patients admitted to public services because in private hospitals they are not allowed to impose compulsory treatment. If cases belonging to the “non-recruited” group were the more severe patients, I would expect them to be admitted more frequently in public hospitals.

Cases who have been recruited were more likely to be selected in public hospital settings rather than in outpatient services compared to those

who were not recruited (Pearson $\chi^2=19.7, df=2, p<0.001$) but this is not an effect of a different symptom severity. Generally, patients were more open to be assessed while they were admitted at the hospital because the research team used to reach them and to spend some time with them and so they were more likely to cooperate.

When cases were identified by screening the outpatient services and they were asked by the research team to join the study they were more reluctant to reach the service to go through the interview. For this reason I do not think that a selection bias might have occurred because of genuine differences in symptom severity or because of different characteristics between recruited and not recruited cases

In this study the recruitment of controls has been challenging.

A sample of individuals aged 18–64 years was recruited from the population of the same geographical areas as the cases. The recruitment was carried out by advertising and leaflets. An effort has been made to get a representative sample of the general population of healthy controls who were selected by quota sampling method.

The control sample was similar, according to the last Italian census data (2011) on a number of socio-demographic factors (age, gender, migrant status, level of education) to the population the cases come from.

There are some differences in terms of mean age and socio-demographic features between cases and controls. Mean age of cases and controls was significantly different ($p<0.01$) so all the analyses were adjusted taking into account age as a confounder in the logistic regression. Other socio-demographic factors (level of education, employment, relationship status) were different in cases and controls so I applied logistic regression to control for those differences. I analysed a small sample of controls and this can limit the validity of results for those variables which exposure is rare (e.g. sexual abuse). However power calculation indicated that the sample of cases and controls was sufficient to detect a modest effect of sexual abuse.

Cases had a significantly lower mean IQ (mean 78.7, sd: 16.8) than controls IQ (mean 101.6, sd: 23) ($p < 0.01$). This magnitude of difference may reflect a limitation of the study methodology because cases were often assessed early when they were still unwell and just a few days after the admission to the hospital. We tried to contact them after discharge but most of them were not interested in coming back to be interviewed again. So the gap between cases and control in the mean IQ probably does not reflect a reliable difference.

There are a few limitations about the possibility to draw definite conclusions about the risk of cannabis exposure on psychosis in this sample.

An issue is that lifetime cannabis consumption among controls is reported by more than a half of the sample (57%) and cannabis consumption in the previous month is 21%. The lifetime prevalence of cannabis consumption in Italy as reported by the GPS-ITA study (22.4%) and by the Milan survey (31.7%) and the cannabis consumption in the previous month, 3% (GPS-ITA) and 7.4% (Milan survey) are lower than cannabis use in our control sample. This may raise the issue of a selection bias of controls and their representativeness of the general population. However, the leaflet and the advertisement for controls recruitment did not mention cannabis use at all, so that it is not likely that the way controls were recruited has biased the selection.

Another explanation of this discrepancy is that the general population prevalence of cannabis consumption may be different across different sites in Italy.

Data on cannabis consumption in the general population come from surveys run at the national level. No detailed differences are reported by regions and by sites. In Milan (2007-2010) for example, the prevalence of cannabis consumption was higher than the national one (31.7%).

Sicily, is the first region in Italy for cannabis production; it produces 90% of the total cannabis amount produced in Italy because of a peculiar micro climate which is favorable to grow cannabis. In 2011 in Sicily has

been registered the 91% of the total national cannabis seizure (Chiusolo, D'Onofrio, Dipartimento Politiche Antidroga, 2011). This may lead to a higher availability of cannabis in Palermo illicit drug market.

Another explanation may be that the median age of the sample taken from the general population survey on cannabis use is higher than median age of controls in my sample, so that the likelihood of being exposed to cannabis is increased in Palermo sample because people tend to smoke at younger age. Unfortunately, detailed data on median age of participants in the GPS-ITA study have not been reported.

However, an overestimation of cannabis exposure among healthy controls would have reduced the odds of cannabis use on psychosis so I am confident about the differences in the risk I found.

Another limitation is that in the present study it was not possible to detect an effect of tobacco in psychosis risk. Tobacco exposure was not associated with an increased risk of psychosis after controlling for the main confounders; further, cannabis exposure cannot be distinguished from tobacco because in Palermo sample all the cases and controls exposed to cannabis used to smoke it together with tobacco.

Another source of bias in case-control studies is recall bias because the information is collected after the disease onset.

For cannabis exposure it is unlikely that people under-report cannabis consumption because the prevalence of lifetime cannabis consumption was higher both in cases (44%) and controls (56.7%) than the prevalence reported for the Italian general population (22%).

Sexual traumatic experiences could have been under reported because of the intimate nature of the questions both in cases and controls, so the effect of sexual abuse during childhood might be underreported; however, Fisher and colleagues supported the reliability of retrospective reports of childhood abuse obtained from individuals with psychotic disorders (Fisher, Craig et al. 2011). Another limitation in obtaining a reliable risk effect of childhood traumatic experiences was the sample size. The association between the risk of psychosis and physical abuse was weak

and it will be valuable to confirm this association with a larger sample. Another limitation is represented by the lack of the analysis of a synergistic effect of the different childhood victimization experiences.

6.7 Conclusions and future direction

This study confirms that the incidence of psychosis is lower in Italy than reported in the UK. Age, gender and migration have an effect on the incidence of psychotic disorders. It would be valuable to compare incidence rates in different sites in Italy and in Europe in order to find differences and similarities and to develop hypothesis on the role of risk factors influencing the differences in the rates.

The European network of national schizophrenia networks studying gene-environment interaction (EUGEI) is a large on-going European first episode psychosis study coordinated by Maastricht University (MUMC). It is aimed at identifying the genetic, clinical and environmental determinants and their interactions involved in the development, severity and outcome of schizophrenia (<http://www.eu-gei.eu/about-the-project>). It will also compare differences in incidence rates across several sites in Europe and it will provide data about differences and similarities across countries.

Migration is confirmed as a risk factor for psychosis in Palermo sample. However, further studies are needed to explore the role of social factors as social disadvantage (Morgan, Kirkbride et al., 2008) mediating this association.

The EUGEI study will provide details on psychosocial factors associated to the risk of developing psychosis at an individual, neighbourhood and social level (e.g. exposure to childhood trauma, substance consumption, measures of social deprivation, social fragmentation, migration history) so I'll have the chance to replicate some of the findings of this case-control study in a larger sample of cases and controls.

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Appendix I

Classification of Psychotic disorders according to ICD-10

Diagnostic criteria for research

F20 - F29 SCHIZOPHRENIA, SCHIZOTYPAL AND DELUSIONAL DISORDERS

F20 SCHIZOPHRENIA

This overall category includes the common varieties of schizophrenia, together with some less common varieties and closely related disorders.

F20.0 - F20.3

General criteria for Paranoid, Hebephrenic, Catatonic and Undifferentiated type of Schizophrenia:

G1. Either at least one of the syndromes, symptoms and signs listed below under (1), or at least two of the symptoms and signs listed under (2), should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).

(1) At least one of the following:

- a) Thought echo, thought insertion or withdrawal, or thought broadcasting.
- b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.
- c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
- d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).

(2) or at least two of the following:

- e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.
- f) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.
- g) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.
- h) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

G2. Most commonly used exclusion criteria: If the patient also meets criteria for manic

episode (F30) or depressive episode (F32), the criteria listed under G1.1 and G1.2 above must have been met before the disturbance of mood developed.

G3. The disorder is not attributable to organic brain disease or to alcohol- or drug-related intoxication, dependence or withdrawal.

F20.0 Paranoid schizophrenia

A. The general criteria for Schizophrenia (F20.0 - F20.3 above) must be met.

B. Delusions or hallucinations must be prominent (such as delusions of persecution, reference, exalted birth, special mission, bodily change or jealousy; threatening or commanding voices, hallucinations of smell or taste, sexual or other bodily sensations).

C. Flattening or incongruity of affect, catatonic symptoms, or incoherent speech must not dominate the clinical picture, although they may be present to a mild degree.

F20.1 Hebephrenic schizophrenia

A. The general criteria for Schizophrenia (F20.0 - F20.3) above must be met.

B. Either (1) or (2):

(1) Definite and sustained flattening or shallowness of affect;

(2) Definite and sustained incongruity or inappropriateness of affect.

C. Either (1) or (2):

(1) Behaviour which is aimless and disjointed rather than goal-directed;

(2) Definite thought disorder, manifesting as speech which is disjointed, rambling or incoherent.

D. Hallucinations or delusions must not dominate the clinical picture, although they may be present to a mild degree.

F20.2 Catatonic schizophrenia

A. The general criteria for Schizophrenia (F20.0 - F20.3 above) must eventually be met, though this may not be possible initially if the patient is uncommunicative.

B. For a period of at least two weeks one or more of the following catatonic prominent:

(1) Stupor (marked decrease in reactivity to the environment and reduction and activity) or mutism;

(2) Excitement (apparently purposeless motor activity, not influenced by

(3) Posturing (voluntary assumption and maintenance of inappropriate or

(4) Negativism (an apparently motiveless resistance to all instructions or movement in the opposite direction);

(5) Rigidity (maintenance of a rigid posture against efforts to be moved);

(6) Waxy flexibility (maintenance of limbs and body in externally imposed positions)

(7) Command automatism (automatic compliance with instructions).

C. Other possible precipitants of catatonic behaviour, including brain disease and metabolic disturbances, have been excluded.

F20.3 Undifferentiated schizophrenia

A. The general criteria for Schizophrenia (F20.0 - F20.3) above must be met.

B. Either (1) or (2):

(1) There are insufficient symptoms to meet the criteria of any of the sub-types F20.0, .1, .4, or .5;

(2) There are so many symptoms that the criteria for more than one of the subtypes listed in B(1) above are met.

F20.4 Post-schizophrenic depression

A. The general criteria for schizophrenia (F20.0 - F20.3 above) must have been met within the past twelve months, but are not met at the present time.

B. One of F20 G1.2 e, f, g or h must still be present.

C. The depressive symptoms must be sufficiently prolonged, severe and extensive to meet criteria for at least a mild depressive episode (F32.0).

F20.5 Residual schizophrenia

A. The general criteria for Schizophrenia (F20.0 - F20.3 above) must have been met at some time in the past, but are not met at the present time.

B. At least four of the following 'negative' symptoms have been present throughout the previous twelve months:

(1) Psychomotor slowing or underactivity;

(2) Definite blunting of affect;

(3) Passivity and lack of initiative;

(4) Poverty of either the quantity or the content of speech;

(5) Poor non-verbal communication by facial expression, eye contact, voice modulation or posture;

(6) Poor social performance or self-care.

F20.6 Simple schizophrenia

A. Slowly progressive development over a period of at least one year, of all three of the following:

(1) A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of drive and interests, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

(2) Gradual appearance and deepening of "negative" symptoms such as marked apathy, paucity of speech, under- activity, blunting of affect, passivity and lack of initiative, and poor non-verbal communication (by facial expression, eye contact, voice modulation and posture).

(3) Marked decline in social, scholastic, or occupational performance.

B. Absence, at any time, of any symptoms referred to in G1 in F20.0 - F20.3, and of hallucinations or well- formed delusions of any kind, i.e. the subject must never have met the criteria for any other type of schizophrenia, or any other psychotic disorder.

C. Absence of evidence of dementia or any other organic mental disorder listed in section F0.

F20.8 Other schizophrenia

F20.9 Schizophrenia, unspecified

F21 SCHIZOTYPAL DISORDER

A. The subject must have manifested, over a period of at least two years, at least four of the following, either continuously or repeatedly:

(1) Inappropriate or constricted affect, subject appears cold and aloof;

(2) Behaviour or appearance which is odd, eccentric or peculiar;

(3) Poor rapport with others and a tendency to social withdrawal;

(4) Odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms;

(5) Suspiciousness or paranoid ideas;

(6) Ruminations without inner resistance, often with dysmorphophobic, sexual or aggressive contents;

(7) Unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization or derealization;

(8) Vague, circumstantial, metaphorical, over-elaborate or often stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence;

(9) Occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations and delusion-like ideas, usually occurring without external provocation.

B. The subject must never have met the criteria for any disorder in F20 (Schizophrenia).

F22 PERSISTENT DELUSIONAL DISORDERS

F22.0 Delusional disorder

A. The presence of a delusion or a set of related delusions other than those listed as typical schizophrenic under F20 G1.1b or d (i.e. other than completely impossible or culturally inappropriate). The commonest examples are persecutory, grandiose, hypochondriacal, jealous (zelotypic) or erotic delusions.

B.The delusion(s) in A must be present for at least three months.

C.The general criteria for schizophrenia (F20.0 - F20.3) are not fulfilled.

D.Persistent hallucinations in any modality must not be present (but transitory or occasional auditory hallucinations that are not in the third person or giving a running commentary, may be present).

E.Depressive symptoms (or even a depressive episode (F32.-)) may be present intermittently, provided that the delusions persist at times when there is no disturbance of mood.

F. Most commonly used exclusion criteria: There must be no evidence of primary or secondary brain disease as listed under F0, or a psychotic disorder due to psychoactive substance use (F1x.5).

Specification for possible subtypes: The following types may be specified, if desired: persecutory type; litigious type; self-referential type; grandiose type; hypochondriacal (somatic) type; jealous type; erotomanic type.

F22.8 Other persistent delusional disorders

This is a residual category for persistent delusional disorders that do not meet the criteria for delusional disorder (F22.0). Disorders in which delusions are accompanied by persistent hallucinatory voices or by schizophrenic symptoms that are insufficient to meet criteria for schizophrenia (F20.-) should be coded here. Delusional disorders that have lasted for less than three months should, however, be coded, at least temporarily, under F23.-.

F22.9 Persistent delusional disorder, unspecified

F23 ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

G1. An acute onset of delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed two weeks.

G2. If transient states of perplexity, misidentification, or impairment of attention and concentration are present, they do not fulfill the criteria for organically caused clouding of consciousness as specified in F05 A.

G3. The disorder does not meet the symptomatic criteria for manic episode (F30), depressive episode (F32), or recurrent depressive disorder (F33).

G4. No evidence of recent psychoactive substance use sufficient to fulfil the criteria of intoxication (F1x.0), harmful use, (F1x.1), dependence (F1x.2) or withdrawal states (F1x.3 and F1x.4). The continued moderate and largely unchanged use of alcohol or drugs in amounts or frequencies to which the subject is accustomed does not necessarily rule out the use of F23; this must be decided by clinical judgement and the requirements of the research project in question.

G5. Most commonly used exclusion criteria: absence of organic brain disease (F0) or serious metabolic disturbances affecting the central nervous system (this does not include childbirth). A fifth character should be used to specify whether the acute onset

of the disorder is associated with acute stress (occurring within two weeks prior to evidence of first psychotic symptoms).

F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia

A. The general criteria for acute and transient psychotic disorders (F23) must be met.

B. The symptomatology is rapidly changing in both type and intensity from day to day or within the same day.

C. The presence of any type of either hallucinations or delusions, for at least several hours, at any time since the onset of the disorder.

D. Symptoms from at least two of the following categories, occurring at the same time:

(1) Emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability;

(2) Perplexity, or misidentification of people or places;

(3) Increased or decreased motility, to a marked degree.

E. Any of the symptoms listed in Schizophrenia F20, G1.1 and G1.2 that are present, are only present for a minority of the time since the onset, i.e. criterion B of F23.1 is not fulfilled.

F. The total duration of the disorder does not exceed three months.

F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia

A. Criteria A, B, C, and D of acute polymorphic psychotic disorder (F23.0) must be met.

B. Some of the symptoms specified for schizophrenia (F20.0 - F20.3) must have been present for the majority of the time since the onset of the disorder, but not necessarily meeting these criteria completely, i.e. at least any one of the symptoms in F20, G1.1a to G1.2g.

C. The symptoms of schizophrenia in B above do not persist for more than one month.

F23.2 Acute schizophrenia-like psychotic disorder

A. The general criteria for acute and transient psychotic disorders (F23) must be met.

B. The criteria for schizophrenia (F20.0 - F20.3) are met, with exception of the duration criterium.

C. The disorder does not meet the criteria B, C and D for acute polymorphic psychotic disorder (F23.0).

D. The total duration of the disorder does not exceed one month.

F23.3 Other acute predominantly delusional psychotic disorder

A. The general criteria for acute and transient psychotic disorders (F23) must be met.

B. Relatively stable delusions and/or hallucinations are present, but they do not fulfil the symptomatic criteria for schizophrenia (F20.0 - F20.3).

C.The disorder does not meet the criteria for acute polymorphic psychotic disorder (F23.0).

D.The total duration of the disorder does not exceed three months.

F23.8 Other acute and transient psychotic disorders

Any other acute psychotic disorders that are unclassifiable under any other category in F23 (such as acute psychotic states in which definite delusions or hallucinations occur but persist for only small proportions of the time) should be coded here. States of undifferentiated excitement should also be coded here if more detailed information about the patient's mental state is not available, provided that there is no evidence of an organic cause.

F23.9 Acute and transient psychotic disorder, unspecified

F24 INDUCED DELUSIONAL DISORDER

A.The subject must develop a delusion or delusional system originally held by someone else with a disorder classified in F20-F23.

B.The two people must have an unusually close relationship with one another, and be relatively isolated from other people.

C.The subject must not have held the belief in question prior to contact with the other person, and must not have suffered from any other disorder classified in F20-F23 in the past.

F25 SCHIZOAFFECTIVE DISORDERS

Note: This diagnosis depends upon an approximate "balance" between the number, severity and duration of the schizophrenic and affective symptoms.

G1. The disorder meets the criteria of one of the affective disorders of moderate or severe degree, as specified for each sub-type.

G2. Symptoms from at least one of the symptom groups listed below, clearly present for most of the time during a period of at least two weeks (these groups are almost the same as for schizophrenia (F20.0 - F20.3)):

(1) Thought echo, thought insertion or withdrawal, thought broadcasting (F20 G1.1a)

(2) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations (F20 G1.1b)

(3) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves; or other types of hallucinatory voices coming from some part of the body (F20 G1.1c)

(4) Persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory (F20 G1.1d), e.g. has visited other worlds; can control the clouds by breathing in and out; can communicate with plants or animals without speaking, etc.

(5) Grossly irrelevant or incoherent speech, or frequent use of neologisms (a marked form of F20 G1.2f)

(6) The intermittent but frequent appearance of some forms of catatonic behaviour,

such as posturing, waxy flexibility and negativism (F20 G1.2g)

G3. Criteria G1 and G2 must be met within the same episode of the disorder, and concurrently for at least some time of the episode. Symptoms from both criteria G1 and G2 must be prominent in the clinical picture.

G4. Most commonly used exclusion criteria: the disorder is not attributable to organic brain disease (in the sense of F0), or to psychoactive substance-related intoxication, dependence or withdrawal (F1).

F25.0 Schizoaffective disorder, manic type

A. The general criteria for schizoaffective disorder (F25) must be met.

B. Criteria of a manic disorder must be met (F30.1 or F31.1).

F25.1 Schizoaffective disorder, depressive type

A. The general criteria schizoaffective disorder (F25) must be met.

B. The criteria for depressive disorder, at least moderate severity must be met (F32.1, F32.2, F31.3 or F31.4).

F25.2 Schizoaffective disorder, mixed type

A. The general criteria for schizoaffective disorder (F25) must be met.

B. The criteria for mixed bipolar affective disorder must be met (F31.6).

F25.8 Other schizoaffective disorders

F25.9 Schizoaffective disorder, unspecified

F28 OTHER NONORGANIC PSYCHOTIC DISORDERS

Psychotic disorders that do not meet the criteria for schizophrenia (F20.-) or for psychotic types of mood [affective] disorders (F30-F39), and psychotic disorders that do not meet the symptomatic criteria for persistent delusional disorder (F22.-) should be coded here (such as persistent hallucinatory disorder). Include here also combinations of symptoms not covered by the previous categories of F20, such as delusions other than those listed as typical schizophrenic under F20 G1.1.b or d (i.e. other than completely impossible or culturally inappropriate) plus catatonia.

F29 UNSPECIFIED NONORGANIC PSYCHOSIS

F30 - F39 MOOD [AFFECTIVE] DISORDERS

F30 MANIC EPISODE

F30.0 Hypomania

A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least four consecutive days.

B. At least three of the following must be present, leading to some interference with personal functioning in daily living:

- (1) increased activity or physical restlessness;
- (2) increased talkativeness;
- (3) difficulty in concentration or distractibility;
- (4) decreased need for sleep;
- (5) increased sexual energy;
- (6) mild spending sprees, or other types of reckless or irresponsible behaviour;
- (7) increased sociability or over-familiarity.

C. The episode does not meet the criteria for mania (F30.1 and F30.2), bipolar affective disorder (F31.-), depressive episode (F32.-), cyclothymia (F34.0) or anorexia nervosa (F50.0).

D. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

F30.1 Mania without psychotic symptoms

A. A mood which is predominantly elevated, expansive or irritable and definitely abnormal for the individual concerned. This mood change must be prominent and sustained for at least a week (unless it is severe enough to require hospital admission).

At least three of the following must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living:

- (1) Increased activity or physical restlessness;
- (2) Increased talkativeness ('pressure of speech');
- (3) Flight of ideas or the subjective experience of thoughts racing;
- (4) Loss of normal social inhibitions resulting in behaviour which is inappropriate to the circumstances;
- (5) Decreased need for sleep;
- (6) Inflated self-esteem or grandiosity;
- (7) Distractibility or constant changes in activity or plans;
- (8) Behaviour which is foolhardy or reckless and whose risks the subject does not recognize e.g. spending sprees, foolish enterprises, reckless driving;
- (9) Marked sexual energy or sexual indiscretions.

C. The absence of hallucinations or delusions, although perceptual disorders may occur (e.g. subjective hyperacusis, appreciation of colours as specially vivid, etc.).

D. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

F30.2 Mania with psychotic symptoms

A.The episode meets the criteria for mania without psychotic symptoms (F30.1) with exception of criterion C.

B.The episode does not simultaneously meet the criteria for schizophrenia (F20) or schizo-affective disorder, manic type (F25.0).

C.Delusions or hallucinations are present, other than those listed as typical schizophrenic in F20 G1.1b, c and d (i.e. delusions other than those that are completely impossible or culturally inappropriate and hallucinations, that are not in the third person or giving a running commentary). The commonest examples are those with grandiose, self-referential, erotic or persecutory content.

D.Mot commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

A fifth character may be used to specify whether the hallucinations or delusions are congruent or incongruent with the mood:

F30.20 mania with mood congruent psychotic symptoms (such as grandiose delusions or voices telling the subject that he has superhuman powers)

F30.21 mania with mood incongruent psychotic symptoms (such as voices speaking to the subject about affectively neutral topics, or delusions of reference or persecution).

F30.8 Other manic episodes

F30.9 Manic episode, unspecified

F31 BIPOLAR AFFECTIVE DISORDER

Note: Episodes are demarcated by a switch to an episode of opposite or mixed polarity or by a remission.

F31.0 Bipolar affective disorder, current episode hypomanic

A.The current episode meets the criteria for hypomania (F30.0).

B.There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms

A.The current episode meets the criteria for mania without psychotic symptoms (F30.1).

B.There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms

A.The current episode meets the criteria for mania with psychotic symptoms (F30.2).

B.There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), depressive episode (F32.-) or mixed affective episode (F38.00).

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:

F31.20 with mood congruent psychotic symptoms

F31.21 with mood incongruent psychotic symptoms

F31.3 Bipolar affective disorder, current episode moderate or mild depression

A.The current episode meets the criteria for a depressive episode of either mild (F32.0) or moderate severity (F32.1).

B.There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode (F30.-), or mixed affective episode (F38.00).

A fifth character may be used to specify the presence of the somatic syndrome as defined in F32, in the current episode of depression:

F31.30 without somatic syndrome

F31.31 with somatic syndrome

F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms

A.The current episode meets the criteria for a severe depressive episode without psychotic symptoms (F32.2).

B.There has been at least one well authenticated hypomanic or manic episode (F30.-) or mixed affective episode (F38.00) in the past.

F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms

A.The current episode meets the criteria for a severe depressive episode with psychotic symptoms (F32.3).

B.There has been at least one well authenticated hypomanic or manic episode (F30.-) or mixed affective episode (F38.00) in the past.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood.

F31.50 with mood congruent psychotic symptoms

F31.51 with mood incongruent psychotic symptoms

F31.6 Bipolar affective disorder, current episode mixed

A.The current episode is characterized by either a mixture or a rapid alternation (i.e. within a few hours) of hypomanic, manic and depressive symptoms.

B.Both manic and depressive symptoms must be prominent most of the time during a period of at least two weeks.

C.There has been at least one well authenticated hypomanic or manic episode (F30.-),

depressive (F32.-) or mixed affective episode (F38.00) in the past.

F31.7 Bipolar affective disorder, currently in remission

A. The current state does not meet the criteria for depressive or manic episode in any severity, or for any other mood disorder in F3 (possibly because of treatment to reduce the risk of future episodes).

B. There has been at least one well authenticated hypomanic or manic episode (F30.-) in the past and in addition at least one other affective episode (hypomanic or manic (F30.-), depressive (F32.-), or mixed (F38.00)).

F31.8 Other bipolar affective disorders

F31.9 Bipolar affective disorders, unspecified

F32 DEPRESSIVE EPISODE

G1. The depressive episode should last for at least 2 weeks.

G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30.-) at any time in the individual's life.

G3. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10- F19) or to any organic mental disorder (in the sense of F00-F09).

Somatic syndrome

Some depressive symptoms are widely regarded as having special clinical significance and are here called "somatic". (Terms such as biological, vital, melancholic, or endogenomorphic are used for this syndrome in other classification.)

A fifth character (as indicated in F31.3; F32.0 and F32.1; F33.0 and F33.1) may be used to specify the presence or absence of the somatic syndrome.

To qualify for the somatic syndrome, four of the following symptoms should be present

- (1) marked loss of interest or pleasure in activities that are normally pleasurable;
- (2) lack of emotional reactions to events or activities that normally produce an emotional response;
- (3) waking in the morning 2 hours or more before the usual time;
- (4) depression worse in the morning;
- (5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people);
- (6) marked loss of appetite;
- (7) weight loss (5% or more of body weight in the past month);
- (8) marked loss of libido.

F32.0 Mild depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the following three symptoms must be present:

(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.

(2) loss of interest or pleasure in activities that are normally pleasurable;

(3) decreased energy or increased fatiguability.

C. An additional symptom or symptoms from the following list should be present, to give a total of at least four:

(1) loss of confidence and self-esteem;

(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt;

(3) recurrent thoughts of death or suicide, or any suicidal behaviour;

(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation;

(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);

(6) sleep disturbance of any type;

(7) change in appetite (decrease or increase) with corresponding weight change).

A fifth character may be used to specify the presence or absence of the "somatic syndrome" (defined on page xx):

F32.00 Without somatic syndrome

F32.01 With somatic syndrome

F32.1 Moderate depressive episode

A. The general criteria for depressive episode (F32) must be met.

B. At least two of the three symptoms listed for F32.0, criterion B, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least six .

A fifth character may be used to specify the presence or absence of the "somatic syndrome" as defined on page xx:

F32.10 Without somatic syndrome

F32.11 With somatic syndrome

F32.2 Severe depressive episode without psychotic symptoms

Note: If important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of

severe episode may still be justified in such a case.

A. The general criteria for depressive episode (F32) must be met.

B. All three of the symptoms in criterion B, F32.0, must be present.

C. Additional symptoms from F32.0, criterion C, must be present, to give a total of at least eight.

D. There must be no hallucinations, delusions, or depressive stupor.

F32.3 Severe depressive episode with psychotic symptoms

A. The general criteria for depressive episode (F32) must be met.

B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D.

C. The criteria for schizophrenia (F20.-) or schizoaffective disorder, depressive type (F25.1) are not met.

D. Either of the following must be present:

(1) delusions or hallucinations, other than those listed as typically schizophrenic in F20, criterion G1(1)b, c, and d (i.e. delusions other than those that are completely impossible or culturally inappropriate and hallucinations that are not in the third person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content;

(2) depressive stupor.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with mood:

F32.30 With mood-congruent psychotic symptoms (i.e. delusions of guilt, worthlessness, bodily disease, or impending disaster, derisive or condemnatory auditory hallucinations)

F32.31 With mood-incongruent psychotic symptoms (i.e. persecutory or self-referential delusions and hallucinations without an affective content)

F32.8 Other depressive episodes

Episodes should be included here which do not fit the descriptions given for depressive episodes in F32.0-F32.3, but for which the overall diagnostic impression indicates that they are depressive in nature. Examples include fluctuating mixtures of depressive symptoms (particularly those of the somatic syndrome) with non-diagnostic symptoms such as tension, worry, and distress, and mixtures of somatic depressive symptoms with persistent pain or fatigue not due to organic causes (as sometimes seen in general hospital services).

F32.9 Depressive episode, unspecified

F33 Recurrent depressive disorder

G1. There has been at least one previous episode, mild (F32.0), moderate (F32.1), or

severe (F32.2 or F32.3), lasting a minimum of 2 weeks and separated from the current episode by at least 2 months free from any significant mood symptoms.

G2. At no time in the past has there been an episode meeting the criteria for hypomanic or manic episode (F30.-).

G3. Most commonly used exclusion criteria: the episode is not attributable to psychoactive substance use (F1) or any organic mental disorder, in the sense of F0.

It is recommended to specify the predominant type of previous episodes (mild, moderate, severe, uncertain).

F33.0 Recurrent depressive disorder, current episode mild

A. The general criteria for recurrent depressive disorder (F33) are met.

B. The current episode meets the criteria for depressive episode, mild severity (F32.0).
A fifth character may be used to specify the presence of the somatic syndrome, as defined in F32, in the

current episode:

F33.00 without somatic syndrome

F33.01 with somatic syndrome

F33.1 Recurrent depressive disorder, current episode moderate

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for depressive episode, moderate severity (F32.1).

A fifth character may be used to specify the presence of the somatic syndrome, as defined in F32, in the current episode:

F33.10 without somatic syndrome

F33.11 with somatic syndrome

F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for severe depressive episode without psychotic symptoms (F32.2).

F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms

A. The general criteria for recurrent depressive disorders (F33) are met.

B. The current episode meets the criteria for severe depressive episode with psychotic symptoms (F32.3).

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:

F33.30 with mood congruent psychotic symptoms

F33.31 with mood incongruent psychotic symptoms

F33.4 Recurrent depressive disorder, currently in remission

A. The general criteria for recurrent depressive disorder (F33) have been met in the past.

B. The current state does not meet the criteria for a depressive episode (F32.-) of any severity, or for any other disorder in F3 (the patient may receive treatment to reduce the risk of further episodes).

F33.8 Other recurrent depressive disorders

F33.9 Recurrent depressive disorder, unspecified

Appendix II

Palermo population aged 18-65 years and split by age-bands, gender and migrant status

Ageband	Gender	Migration	Palermo Population	Denominator years	x 3
18-24	female	migrant	686		2058
25-29	female	migrant	1007		3021
30-34	female	migrant	1277		3831
35-39	female	migrant	1151		3453
40-44	female	migrant	1137		3411
45-49	female	migrant	1001		3003
50-54	female	migrant	693		2079
55-59	female	migrant	383		1149
60-65	female	migrant	207		621
18-24	male	migrant	793		2379
25-29	male	migrant	1011		3033
30-34	male	migrant	1462		4386
35-39	male	migrant	1313		3939
40-44	male	migrant	1119		3357
45-49	male	migrant	878		2634
50-54	male	migrant	602		1806
55-59	male	migrant	287		861
60-65	male	migrant	135		405
18-24	female	native	29717		89151
25-29	female	native	18992		56976
30-34	female	native	20256		60768
35-39	female	native	23062		69186
40-44	female	native	24403		73209
45-49	female	native	25564		76692
50-54	female	native	23920		71760
55-59	female	native	22466		67398
60-65	female	native	26157		78471
18-24	male	native	27999		83997
25-29	male	native	19775		59325
30-34	male	native	18462		58386
35-39	male	native	21690		65070
40-44	male	native	22296		66888
45-49	male	native	22869		68607
50-54	male	native	21011		63033
55-59	male	native	19980		59940
60-65	male	native	23152		69456

1.283.739

Appendix III

Cannabis Experience Questionnaire

GAP/IMPACT		ID NUMBER: ____
SUBJECT'S INITIALS:	DATE OF COMPLETION:	STUDY PERIOD: __
RATER'S INITIALS: __	__ / __ / ____	00=Baseline
		03=3 Months Follow-up

Cannabis Experiences Questionnaire (CEQ4)

Emma Barkus, John Stirling and Shôn Lewis
(Modified by GAP & IMPACT)

Thank you for giving your time to complete this questionnaire.

Section 1. Please tick as appropriate.

1. Have you ever smoked/used cannabis?

- ☐ YES (If yes, go to question 2)
- ☐ NO (If no, please go to section 5)

2. How old were you when you first tried cannabis?

.....

☐ Why did you first try cannabis?

- ☐ My friends were using it
- ☐ My family members were using it
- ☐ To self Medicate from either physical or psychological discomfort
- ☐ Other (please explain)

4. Do you currently use cannabis?

- ☐ YES
- ☐ NO

If no, at what age did you stop?.....

Please state the reason why you stopped.

5. If Yes to 4. Why do you continue to use cannabis? (You can tick more than one box)

- ☐ I like the effect, it gives me a buzz
- ☐ It makes me feel relaxed
- ☐ It makes me feel less anxious
- ☐ It makes me feel more sociable
- ☐ Other (please explain).....

6. Does/did cannabis affect your health in any way?

- ☐ YES (If yes, please explain).....
- ☐ NO

7. Does/did cannabis make social situations easier?

- ☐ YES (If yes, please explain how?
- ☐ NO

8. Would you like to stop using cannabis one day?

- ☐ YES (If yes, please explain why?).....
- ☐ NO
- ☐ I have already stopped

9. How do/did you mostly use cannabis?

- ☐ I smoke it in a joint with tobacco
- ☐ I smoke it in a joint without tobacco
- ☐ I smoke it using a bong
- ☐ I eat or drink it
- ☐ Other (please explain).....

10. How often do/did you use cannabis?

- ☐ Every day
- ☐ More than once a week
- ☐ About once a week
- ☐ About once/twice a month
- ☐ A few times each year
- ☐ About once a year
- ☐ I have only used cannabis once or twice

11. When do/did you mostly use cannabis?

- ☐ At weekends
- ☐ During the day
- ☐ During the evening
- ☐ During the day and evening
- ☐ Other (please explain).....

12. Do you/did you mostly use cannabis:

- ☐ Socially (with friends)
- ☐ On my own
- ☐ Both

13. On average how much money per week do/did you usually spend on cannabis?

- | | | |
|--|-------------------------------------|------------------------------------|
| <input type="checkbox"/> Less than £2.50 | <input type="checkbox"/> £2.50 - £5 | <input type="checkbox"/> £6 - £10 |
| <input type="checkbox"/> £11 - £15 | <input type="checkbox"/> £16 - £20 | <input type="checkbox"/> Above £20 |

14. What type of cannabis do/did you mostly use?

- ☐ Hash (cannabis resin/solid)
- ☐ Imported herbal cannabis
- ☐ Home-grown skunk/ Sinsemilla
- ☐ Super skunk
- ☐ Other (please state).....

Section 2. Have you had these experiences while smoking cannabis? If so please also rate whether it was a good, bad or neutral experience

	Rarely or never	From time to time	Sometimes	More often than not	Almost always	Good? (G) Bad? (B) Neutral? (N)
Fearful						
Feel like going crazy/mad						
Nervy						
Suspicious						
Feeling happy						
Full of plans/ideas						
Hearing voices						
Able to understand the world better						
Seeing visions						
Time feels longer						

Section 3. How often have you had these experiences after the initial effects of cannabis have worn off? Please also rate whether it was a good, bad or neutral experience.

	Rarely or never	From time to time	Sometimes	More often than not	Almost always	Good? (G) Bad? (B) Neutral? (N)
Not wanting to do anything						
Being suspicious without reason						
Slowed down thinking						
Difficulty in concentrating						
Not able to think clearly						

Section 4.

Please tell us in the table below of any other drug(s) (including alcohol and tobacco) which you use/have used in the past. Also please state how often you use/have used it, the age at which you first tried the drug(s) and whether you are a past or current user. Use a new box for each additional drug. Circle your response(s) as appropriate.

Drug	Frequency	Age	Use	When
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'	When started When stopped	Current Past	Day Night Both day and night
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'		Current Past	Day Night Both day and night
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'		Current Past	Day Night Both day and night

Drug	Frequency	Age	Use	When
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'	When started When stopped	Current Past	Day Night Both day and night
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'		Current Past	Day Night Both day and night
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'		Current Past	Day Night Both day and night
	Every day More than once a week A few times each month A few times each year Only once or twice Units (alcohol) or expenditure (drugs) in an average session'		Current Past	Day Night Both day and night

Section 5. Life Time Cannabis History questionnaire, self administered.
(adapted from the LH Alcohol Q-4)

Age range (younger to older)	Frequency	Quantity (average xday)	Type	Setting of use
0 to 17	<input type="checkbox"/> Every day <input type="checkbox"/> More than once a week <input type="checkbox"/> About once a week <input type="checkbox"/> About once/twice a month <input type="checkbox"/> A few times each year <input type="checkbox"/> About once a year <input type="checkbox"/> I have only used cannabis once or twice	<input type="checkbox"/> 1 joint <input type="checkbox"/> 2 to 3 joints <input type="checkbox"/> 4 or more joints Mostly shared: <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Hash (cannabis resin/solid) <input type="checkbox"/> Imported herbal cannabis <input type="checkbox"/> skunk/ Sensimilla <input type="checkbox"/> Super skunk <input type="checkbox"/> Other	<input type="checkbox"/> Socially (with friends) <input type="checkbox"/> On my own <input type="checkbox"/> Both
18 to 20	<input type="checkbox"/> Every day <input type="checkbox"/> More than once a week <input type="checkbox"/> About once a week <input type="checkbox"/> About once/twice a month <input type="checkbox"/> A few times each year <input type="checkbox"/> About once a year <input type="checkbox"/> I have only used cannabis once or twice	<input type="checkbox"/> 1 joint <input type="checkbox"/> 2 to 3 joints <input type="checkbox"/> 4 or more joints Mostly shared: <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Hash (cannabis resin/solid) <input type="checkbox"/> Imported herbal cannabis <input type="checkbox"/> skunk/ Sensimilla <input type="checkbox"/> Super skunk <input type="checkbox"/> Other	<input type="checkbox"/> Socially (with friends) <input type="checkbox"/> On my own <input type="checkbox"/> Both

Above 21	<input type="checkbox"/> Every day <input type="checkbox"/> More than once a week <input type="checkbox"/> About once a week <input type="checkbox"/> About once/twice a month <input type="checkbox"/> A few times each year <input type="checkbox"/> About once a year <input type="checkbox"/> I have only used cannabis once or twice	<input type="checkbox"/> 1 joint <input type="checkbox"/> 2 to 3 joints <input type="checkbox"/> 4 or more joints Mostly shared: <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Hash (cannabis resin/solid) <input type="checkbox"/> Imported herbal cannabis <input type="checkbox"/> skunk/ Sensimilla <input type="checkbox"/> Super skunk <input type="checkbox"/> Other	<input type="checkbox"/> Socially (with friends) <input type="checkbox"/> On my own <input type="checkbox"/> Both
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Appendix IV

Social Data Schedule

SOCIAL DATA- Page 1 of 12
Apr 08a

GAP/IMPACT		ID NUMBER: ____
SUBJECT'S INITIALS:	DATE OF COMPLETION:	STUDY PERIOD: __
RATER'S INITIALS: __	__ / __ / ____	00=Baseline
		03=3 Months Follow-up

SOCIAL DATA SCHEDULE

PART A. SOCIODEMOGRAPHIC CHARACTERISTICS

1) Sex

- 0 Male
1 Female

☐

2) Date of birth

--	--	--	--	--	--	--	--

3) Age

--	--

4) From the list below, how would you describe your ethnicity?

- 0 White British
1 Mixed
2 Indian
3 Pakistani
4 Bangladeshi
5 Other Asian
6 Black Caribbean
7 Black African
8 Black Other
9 Chinese
10 Other (specify)

--	--

.....

5) Where did you live for the first 16 years of your life, starting with the place you were born?

Country	City/Town	Street	No. of years
.....
.....
.....
.....
.....
.....

6) With whom do you live now?

- 0 Alone
- 1 Alone, with children
- 2 Partner/Spouse
- 3 Partner/Spouse and children
- 4 Parents
- 5 Other family
- 6 Friends
- 7 Other (specify)

☐

.....

7) With whom did you live one year ago?

- 0 Alone
- 1 Alone, with children
- 2 Partner
- 3 Partner and children
- 4 Parents
- 5 Other family
- 6 Friends
- 7 Other (specify)

☐

.....

8) With whom did you live five years ago?

- 0 Alone
- 1 Alone, with children
- 2 Partner
- 3 Partner and children
- 4 Parents
- 5 Other family
- 6 Friends
- 7 Other (specify)

☐

9) Since leaving your parents' home, have you ever lived with others?

- 0 No
- 1 Yes
- 99 Not applicable

☐

10) What is your relationship status now?

- 0 Single
- 1 Married/Living with someone
- 2 In steady relationship
- 3 Divorced, Separated
- 4 Widowed

☐

11) What was your relationship status one year ago?

- 0 Single
- 1 Married/Living with someone
- 2 In steady relationship
- 3 Divorced, Separated
- 4 Widowed

☐

12) What was your relationship status five years ago?

- 0 Single
- 1 Married/Living with someone
- 2 In steady relationship
- 3 Divorced, Separated
- 4 Widowed

☐

13) Have you ever been in a long-term relationship (1 or more years)?

- 0 No
- 1 Yes

☐

14) What was the highest level of education you reached?

- 0 No qualifications
- 1 GCSE/O' levels
- 2 A' levels
- 3 Vocational/college (B. Tecs/NVQs etc.)
- 4 University/Professional Qualifications

☐

15) Are you employed now?

- 0 No, unemployed
- 1 No, student
- 2 Yes, full-time
- 3 Yes, part-time

☐

If yes, position held:

.....

16) Were you employed one year ago?

- 0 No, unemployed
- 1 No, student
- 2 Yes, full-time
- 3 Yes, part-time

☐

If yes, position held:

.....

17) Were you employed five years ago?

- 0 No, unemployed
- 1 No, student
- 2 Yes, full-time
- 3 Yes, part-time

☐

If yes, position held:

.....

18) Have you ever been employed?

- 0 No
- 1 Yes

☐

19) What is your first language?

- 0 English
- 1 Other (please state) _ _ _ _ _

☐

20) What was your fathers main job at the time of your birth?

21) Do you have any close confidants?

0 No
1 Yes

☐

PART B. INTRUSIVE LIFE EVENTS

I would now like to ask you about things that may have happened to you or problems you may have faced throughout your life. SHOW CARD.

1) Looking at the list above, can you tell me if you have ever suffered from any of the problems or events shown on the card, at any time in your life?

(If YES, please specify the approximate date that these incidences occurred. **IF ONE OFF INCIDENT THEN RECORD FROM AND TO DATES AS THE SAME.**)

a) Serious injury or assault to yourself YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

b) Bullying YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

c) Violence at work YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

d) Violence in the home YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

e) Sexual abuse YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

f) Being expelled from school YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

g) Running away from home YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

h) Being homeless YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

i) Taken into local authority care YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

j) Time in children's institution YES / NO

Dates (DD / MMM / YYYY)	
From:	To:

PART C. CHILDHOOD EXPERIENCES

[Selected items from Childhood Experiences of Care & Abuse-Questionnaire (CECA-Q)]

1) WHO BROUGHT YOU UP BEFORE AGE 17?

Write below the PARENT FIGURES who brought you up in childhood. List each family arrangement with different types of parent figures which lasted a year or longer. Consider natural parents, step-parents (including parents' live in partners), aunt, friends of the family, adoptive parents, foster parents, etc.

If you have only lived in one arrangement, then fill in the first family arrangement and leave the other boxes blank. For example, if this was with your natural parents, write in 'Mother' and 'Father' and age '0'.

Family arrangement	Mother figure	Father figure	Your age at start
First (ALL)			

If you have lived in other arrangements such as with mother alone or mother and step-father, then list them below together with age you were when the arrangement began.

Family arrangement	Mother figure	Father figure	Your age at start
Second (If applicable)			
Third (If applicable)			

Were you ever in a children's home or institution prior to age 17?

0 No
1 Yes

☐

If NO, go to question 2.

If yes: Type of institution e.g. local authority care; hospital, etc.	Age entered	Age left

2) PARENTAL LOSS AND SEPARATION

(Please circle or write in answer)

Did either parent die before you were aged 17?

If YES, what age were you?

Have you ever been separated from either parent for 6 months or more before age 17?

Mother		Father	
No	Yes	No	Yes
Age		Age	
No	Yes	No	Yes

If NO, separation, then go to question 3.

If YES, separated:

At what age were you first separated?	Age	Age
How long was this separation for? Years Years
What was the reason for separation?		
Parental illness	No Yes	No Yes
Parental divorce, separation	No Yes	No Yes
Abandoned by parent or never knew parent	No Yes	No Yes
Other reason (please specify below)	No Yes	No Yes

Please describe your experience

.....

.....

3) PHYSICAL PUNISHMENT BEFORE THE AGE OF 17 BY A PARENT FIGURE OR OTHER HOUSEHOLD MEMBER

When you were a child or a teenager were you ever hit repeatedly with an implement such as a belt or stick) or punched, kicked or burnt by someone in the household?

0 No
1 Yes

☐

If NO, go to question 4.

If YES:

	Mother Figure	Father Figure
How old were you when it began?	Age	Age
Did the hitting happen on more than one occasion?	No Yes	No Yes
How were you hit?	0 Belt or stick 1 Punched/kicked 2 Hit with hand 3 Other	0 Belt or stick 1 Punched/kicked 2 Hit with hand 3 Other
Were you ever injured, e.g. bruises, black eyes, broken limbs?	No Yes	No Yes
Was this person ever so angry they seemed out of control?	No Yes	No Yes

Please describe your experience

.....

.....

Did you experience this from anyone else in the household?

0 No
1 Yes

☐

Please describe your experience

.....

.....

.....

.....
4) UNWANTED SEXUAL EXPERIENCES BEFORE AGE 17
 (Please circle as appropriate)

When you were a child or teenager did you ever have any unwanted sexual experiences?

- 0 No
 1 Yes
 2 Unsure

☐

Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17?

- 0 No
 1 Yes
 2 Unsure

☐

Can you think of any upsetting sexual experiences before age 17 with a related adult or someone in authority, e.g. teacher?

- 0 No
 1 Yes
 2 Unsure

☐

If NONE, end interview.

If YES or UNSURE to any of the above, then complete the following:

	First Experience		Second Experience	
How old were you when it began?	Age		Age	
Was the other person someone you knew?	No	Yes	No	Yes
Was the other person a relative?	No	Yes	No	Yes
Did this person do it on more than one occasion?	No	Yes	No	Yes
Did it involve touching private parts of your body?	No	Yes	No	Yes
Did it involve sexual intercourse?	No	Yes	No	Yes

Please describe your experience

.....

.....

Appendix V

Psychosis Screening Questionnaire

GAP/IMPACT		ID NUMBER: _ _ _ _
SUBJECT'S INITIALS: _ _	DATE OF COMPLETION: _ _ / _ _ / _ _	STUDY PERIOD: _ _ 00=Baseline
RATER'S INITIALS: _ _		

Psychosis screening questionnaire

Code: No = 0 Unsure = 1 Yes = 2

In this health survey we have to ask about a whole range of experiences. Some of these experiences are quite rare. However, I would be very much obliged if you would bear with us and answer the questions I am going to ask you now.

- Q1. Over the past year, have there been times when you felt very happy indeed without a break for days on end? ☐
- (a) Was there an obvious reason for this? ☐
- (b) Did your relatives or friends think it was strange or complain about it? ☐ If 2 stop
- Q2. Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person? ☐
- (a) Did this come about in a way that many people would find hard to believe, for instance through telepathy? ☐ If 2 stop

No = 0 Unsure = 1 Yes = 2

- Q3. Over the past year, have there been times when you felt that people were against you? ☐
- (a) Have there been times when you felt that people were deliberately acting to harm you or your interests? ☐
- (b) Have there been times when you felt that a group of people was plotting to cause you serious harm or injury? ☐ If 2 stop
- Q4. Over the past year have there been times when you felt that something strange was going on? ☐
- (a) Did you feel it was so strange that people would find it very hard to believe? ☐ If 2 stop
- Q5. Over the past year, have there been times when you heard or saw things that other people couldn't ☐ If 1 or 2 stop
- (a) Did you at any time hear voices saying quite a few words or sentences when there was no-one around that might account for it? ☐ If 2 stop
- Q6. Have you ever received treatment for any psychiatric or psychological problem?
-
-